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Polygenic risk for psychiatric disorder and singleness in patients with severe mental illness and controls

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ABSTRACT

We aimed to investigate whether the polygenic risk score (PRS) for schizophrenia influences time in couple relationships for patients with severe mental illness and controls. We combined the nationwide Danish registers with genetic information from dried neonatal blood spots. We included 2,599 individuals with schizophrenia, 1,446 with bipolar disorder, 20,315 with depression, and 6,963 controls. PRS for schizophrenia, depression, and bipolar disorder were estimated using data from the Psychiatric Genetics Consortium and analyzed both as a scale-predictor and as highest versus other deciles. The main outcome was number of days in couple relationships. Patients with schizophrenia had markedly fewer days/year in couple relationships: 64 (95% CI; 61–69) than patients with depression: 119 (95% CI; 117–121), bipolar disorder: 103 (95% CI 97–110), and controls: 136 (95% CI 133–139). PRS for schizophrenia was associated with fewer days in couple relationships in patients with schizophrenia (scale-PRS: IRR = 0.95 (0.93–0.97)) or depression (highest decile: IRR = 0.93 (0.87–0.98)). PRS for bipolar disorder (as scale) was also associated with fewer days in couple relationships in patients with depression (IRR = 0.99 (0.99–1.00)) or bipolar disorder (IRR = 0.96 (0.94–0.99)) and controls (IRR = 0.99 (0.97–1.00), and IRR = 0.89 (0.81–0.98) for the highest decile). Due to the number of statistical tests, however, it cannot be concluded definitely that some of these may not be spurious findings. In conclusion, our findings implicate high genetic loading for schizophrenia as a predisposing factor to singleness in patients with schizophrenia or depression, and genetic loading for bipolar disorder a similar predisposing factor in patients with depression, bipolar disorder or controls.

1. Introduction

Singleness is a risk factor for severe mental disorder, but the relationship between severe mental disorder and singleness is complex and depends on which of the severe mental disorders that are under study. For schizophrenia, a particularly robust relationship exists, since singleness increases the risk of schizophrenia, and since schizophrenia subsequently increases the risk of singleness as well (Agerbo et al., 2004). Other studies support that individuals who have been admitted to a psychiatric hospital with schizophrenia are subsequently at increased risk to become single (Munk-Jorgensen and Mortensen, 1992; Salokangas et al., 2001). Furthermore, it is plausible that schizophrenia hinders social achievement long before the first admission (Agerbo et al., 2004). Thus, prospective research suggests that poor premorbid social functioning constitutes a marker of illness vulnerability in the schizophrenia spectrum (Schiffman et al., 2004; Tsuji et al., 2013; Zammit et al., 2004). For major depression and bipolar disorder, a cross-national study suggests that being divorced or separated is associated with higher rates of major depression than among married persons (Weissman et al., 1996), and bipolar disorder is associated with an unusually high divorce rate (Granek et al., 2016).

Given the poor premorbid adjustment in schizophrenia (Agerbo et al., 2004; Mortensen et al., 2005; Sørensen et al., 2018; Urfer-Parnas et al., 2010), it is likely that patients with schizophrenia have spent much less time in couple relationships than patients with unipolar depression or bipolar disorder by the time they receive their diagnosis.

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However, the extent to which such differences in singleness exists between major psychiatric disease categories has not been estimated in large-scale studies. Moreover, the possible genetic underpinnings of such differences have also not been studied in any detail. A link between severe mental illness such as schizophrenia, bipolar disorder and unipolar depression and singleness could be due solely to disease-specific factors, but it is also possible that it could be due to genetic factors, e.g. reflecting personality traits and liability for symptoms outside the underlying disorder (e.g. genetic risk of depression among patients with schizophrenia). Cross-disorder effects can, for instance, be examined using polygenic risk-score analyses from a broader set of common variants (Smoller et al., 2013). In essence, the polygenic risk score is a sum of trait-associated alleles across many genetic loci and their associated weights, generally weighted by effect sizes estimated from a genome-wide association study (GWAS) (Agerbo et al., 2015; Dudbridge, 2013; Euesden et al., 2015). For instance,PRS for schizophrenia (Ripke et al., 2014), bipolar disorder (Purcell et al., 2009) and unipolar disorder (Smoller et al., 2013) have been developed and described. A better understanding of the relationships between PRS and social functioning might contribute to understanding the genetic architecture of the disorders and their sub-phenotypes.

The primary aim of the current study was to investigate the possible effect of PRS for schizophrenia, PRS on bipolar disorder and PRS for unipolar disorder on the time spent in couple relationships in cohorts of patients with schizophrenia, unipolar depression, bipolar disorder and controls. We wanted to answer the following questions: 1) Is PRS for schizophrenia associated with singleness in patients with schizophrenia, bipolar disorder, unipolar depression and controls? And 2) Is PRS for schizophrenia associated more strongly with singleness than the two other PRS? The underlying assumption is 1) that a diagnosis of schizophrenia is more strongly associated with singleness than the 2 other diagnoses and 2) we also hypothesized that PRS for schizophrenia correlates with singleness. This hypothesis was based on recent evidence that higher PRS for schizophrenia has been associated with non-psychotic symptoms including high self-rated scores on “negative symptom“ scales (possibly associated with schizophrenia) and on anxiety (Jones et al., 2016; Kendler, 2016), and more psychiatric hospitalizations (i.e. a measure of chronicity) in schizophrenia (Meier et al., 2016). We examined these hypotheses in large samples of patients with schizophrenia, unipolar depression, bipolar disorder and controls.

2. Methods

2.1. Data sources

This was an observational cohort study linking Danish population-based registers using a unique personal identification number. This identification number has been assigned to all live-born children and new residents in Denmark since 1968 across all registration systems (Pedersen, 2011). The Danish Psychiatric Central Research Register has covered all psychiatric inpatient facilities since 1969 and outpatient contacts since 1995 (Mors et al., 2011). Diagnostic information was based on the ICD-10 from 1994 (WHO, 1993). The Danish Civil Registration System (Pedersen, 2011) contains information on dates of birth, death, immigration, emigrations, and links to family members. The Integrated Database for Longitudinal Labor Market Research covers the entire population and contains yearly information from 1980 including income, marital status, education, and birthplace (Petersson et al., 2011). The Danish Neonatal Screening Biobank stores dried blood spots taken after birth from nearly all infants born in Denmark after 1981 (Pedersen et al., 2018).

2.2. Study population

Based on the Psychiatric Central Research Register, we identified 2,599 individuals with schizophrenia (F20 in ICD-10), 1,446 individuals with bipolar disorder (F30 or F31 in ICD-10), and 20,315 individuals with unipolar depression (F32–F39 in ICD-10), all born since 1981 and with a stored sample of dried neonatal bloodspots in the Danish Newborn Screening Biobank. These numbers deviate slightly from the full number of genotyped individuals previously described, primarily due to censorship due to migration (Pedersen et al., 2018). We also included a set of controls matched on sex and month of birth to the individuals with schizophrenia, and who did not have a diagnosis of schizophrenia, bipolar disorder, unipolar depression, autism, or ADHD. Depending on the number of available matches, up to three controls were selected for each schizophrenia case, for a total of 6,963 controls.

2.3. Outcome: Time in couple relationships

Annual information on marital status was categorized as married and living with spouse, cohabiting and living with cohabitee, or living alone. Being in a couple relationship was based on being married or in a cohabiting relationship (the latter defined as two unrelated people of opposite sex and with an age difference of no more than 15 years, living together, or as two people living together with a common child). We estimated the number of days a person was in a couple relationship, starting at the date of incident psychiatric disorder (or 18th birthday, if diagnosed at an earlier age), and until the end of 2016, after which registers on relationship status were no longer up-to-date.

2.4. Polygenic risk scores

The polygenic risk scores for schizophrenia, bipolar disorder, and unipolar depression were estimated using linkage disequilibrium-pruned data from the Psychiatric Genetics Consortium (excluding the Danish samples) as discovery datasets, and calculated using different thresholds (P(t)) for p-values for the individual single nucleotide polymorphisms (SNPs) (Ripke et al., 2014). Further details of genotyping and QC have previously been published (Pedersen et al., 2018). Genotyping was performed at the Broad Institute of Harvard University and Massachusetts Institute of Technology (Cambridge, MA) using the Infinium PsychChip array, version 1.0 (Illumina CA) according to the manufacturer's protocols (Gunderson et al., 2006). QC and imputation (using 1000 genomes as the reference panel) were conducted using the Ricopili pipeline. For the present paper, we a priori decided to use $p < 0.05$ as the primary cutoff, in line with previous studies (Agerbo et al., 2015; Ripke et al., 2014). We prespecified $p(t) < 0.001$ as a sensitivity analysis and included this data as well as an important prespecified outcome. A total of 10 p(t) cutoffs were available, and all were included in a graphical presentation of p-values. These p(t) values were $p(t) \leq 5*10–8$, $p(t) \leq 1*10–6$, $p(t) \leq 0.0001$, $p(t) \leq 0.001$, $p(t) \leq 0.01$, $p(t) \leq 0.05$, $p(t) \leq 0.1$, $p(t) \leq 0.2$, $p(t) \leq 0.5$, and $p(t) \leq 1$.

2.5. Analyses

Analyses of days in couple relationship were conducted using Poisson regression with robust standard errors. Due to variable follow-up times, we counted the number of days that each individual was under observation (from incident psychiatric disorder or 18th birthday, whichever came last), and used the natural logarithm of this as the offset for the models.

For all analyses, the polygenic risk scores were entered into the models both as scale variables and as a binary variable indicating whether the person was in the highest decile (Y/N) of the polygenic risk score for schizophrenia, bipolar disorder, or unipolar depression.

All models were adjusted for the top four ancestral principal components. All analyses were run both with each PRS entered individually (termed “model 1” in the results), and with all PRS's entered simultaneously and thus mutually adjusted (termed “model 2” in the results).

Table 1
Sample characteristics of the four populations.

	Schizophrenia (n = 2,599)	Unipolar depression (n = 20,315)	Bipolar disorder (n = 1,446)	Controls (n = 6,963)
N (%) Men	1,507 (58.0%)	5,766 (31.5%)	565 (39.1%)	4,018 (57.7%)
Mean (SD) age of onset	21.7 (3.5)	20.5 (3.9)	22.6 (3.9)	21.6 (3.5)*
Cohabiting days/year (95% confidence interval	64.4 (60.5–68.6)	118.8 (117.2–120.5)	103.4 (97.2–109.9)	136.2 (133.2–139.4)

Cohabitation includes marriage. *Defined as age at the matchdate on which the corresponding case with schizophrenia had his or her onset.

3. Results

The study included 2,599 people with incident schizophrenia, 1,446 people with incident bipolar disorder, 20,315 people with incident unipolar depression, and 6,963 controls. Table 1 shows the sample characteristics for the each of the four study populations. The majority of the samples with schizophrenia (58.0%) and matched controls (57.7%) was male, whereas women were more prevalent in the analyses of bipolar disorder (60.9%) and unipolar depression (67.8%). For all three populations, the mean age of onset was in the early twenties, reflecting that this was a rather young sample.

3.1. Association between PRS and time in couple relationships

3.1.1. Population with schizophrenia

The PRS for schizophrenia predicted number of days in couple relationships during follow-up. The number of days/year in cohabiting relationships was reduced by some 20 to 25 percent for people in the highest decile of polygenic risk for schizophrenia (Tables 2 and 3), although this was only statistically significant when using p(t) < 0.001. The same tendency was observed when using the polygenic risk scores for schizophrenia as a scale. Fig. 1 indicates that these results were stable across different p(t)-values. McFadden's pseudo R-squared ranged between 1 and 2%. There were virtually no differences between model 1 and model 2 (in which PRS's were mutually adjusted).

3.1.2. Population with unipolar depression

Among people with unipolar depression, being in the highest decile of polygenic risk for schizophrenia was associated with fewer days in a cohabiting relationship (Tables 2 and 3), although the association was modest at IRR 0.93 (95% CI 0.87–0.98, p < 0. 01) when using p (t) < 0.05. A similar tendency was observed for the polygenic risk scores for bipolar disorder, although only linearly and not when comparing the highest decile of scores to the rest. Increasing polygenic risk score for unipolar depression was not associated with number of days cohabiting for (all p > 0.30). Fig. 1 indicates that these results were stable across different p(t)-values. McFadden's pseudo R-squared was low at around 0.2%. There were virtually no differences between model 1 and model 2 (in which PRS's were mutually adjusted).

Table 2
Polygenic risk scores' association with days in cohabiting relationships. P(threshold) < 0.05 for inclusion in polygenic risk score calculations.

		Model 1[c]	Model 2[c]
Population with schizophrenia			
PRS-SCZ	As scale[a]	0.95 (0.93–0.97), p < 0.001	0.95 (0.93–0.97), p < 0.001
	Highest decile[b]	0.84 (0.68–1.04), p = 0.12	0.84 (0.67–1.05), p = 0.12
PRS-DEP	As scale[a]	1.00 (0.96–1.05), p = 0.85	1.01 (0.97–1.05), p = 0.69
	Highest decile[b]	1.09 (0.90–1.33), p = 0.38	1.10 (0.90–1.33), p = 0.35
PRS-BIP	As scale[a]	0.99 (0.96–1.02), p = 0.42	1.01 (0.98–1.04), p = 0.50
	Highest decile[b]	0.97 (0.78–1.21), p = 0.82	0.99 (0.80–1.24), P = 0.95
Population with unipolar depression			
PRS-SCZ	As scale[a]	1.00 (1.00–1.01), p = 0.23	1.00 (1.00–1.01), p = 0.07
	Highest decile[b]	0.93 (0.87–0.98), p = 0.01	0.93 (0.87–0.99), p = 0.02
PRS-DEP	As scale[a]	0.99 (0.99–1.00), p = 0.31	1.00 (0.99–1.01), p = 0.38
	Highest decile[b]	1.01 (0.96–1.06), p = 0.65	1.01 (0.97–1.06), p = 0.58
PRS-BIP	As scale[a]	0.99 (0.99–1.00), p = 0.02	0.99 (0.98–1.00), p = 0.007
	Highest decile[b]	0.97 (0.92–1.02), p = 0.23	0.98 (0.93–1.03), p = 0.35
Population with bipolar disorder			
PRS-SCZ	As scale[a]	1.00 (0.99–1.02), p = 0.58	1.01 (0.99–1.02), p = 0.28
	Highest decile[b]	0.94 (0.77–1.15), p = 0.58	0.96 (0.78–1.17), p = 0.66
PRS-DEP	As scale[a]	1.00 (0.96–1.04), p = 0.99	1.00 (0.97–1.04), p = 0.83
	Highest decile[b]	0.93 (0.76–1.13), p = 0.44	0.93 (0.77–1.13), p = 0.46
PRS-BIP	As scale[a]	0.96 (0.94–0.99), p = 0.01	0.96 (0.93–0.99), p = 0.007
	Highest decile[b]	0.86 (0.71–1.05), p = 0.15	0.87 (0.71–1.06), p = 0.16
Control population			
PRS-SCZ	As scale[a]	1.00 (0.99–1.00), p = 0.37	1.00 (0.99–1.01), p = 1.00
	Highest decile[b]	0.94 (0.84–1.05), p = 0.27	0.96 (0.86–1.08), p = 0.48
PRS-DEP	As scale[a]	0.99 (0.97–1.00), p = 0.08	0.99 (0.97–1.00), p = 0.13
	Highest decile[b]	0.92 (0.84–1.01), p = 0.09	0.93 (0.85–1.02), p = 0.12
PRS-BIP	As scale[a]	0.99 (0.97–1.00), p = 0.009	0.99 (0.97–1.00), p = 0.02
	Highest decile[b]	0.89 (0.81–0.98), p = 0.02	0.90 (0.81–0.99), p = 0.04

PRS: Polygenic risk score. PRS-SCZ/DEP/BIP: PRS for schizophrenia, unipolar depression, or bipolar disorder, respectively. IRR: Incidence rate ratio. Parentheses are 95% confidence intervals. All models adjusted for the top four ancestral principal components.

[a] IRR reflects a one-point increase in PRS.

[b] Highest decile of PRS versus remaining nine deciles.

[c] In model 1, each PRS is entered individually. In model 2, each PRS is adjusted for the two other PRS's of the same kind – i.e. all "as scale" estimates adjusted for other "as scale" PRS's, and all "highest decile" estimated adjusted for other "highest decile" PRS's.

Table 3
Polygenic risk scores' association with days in cohabiting relationships. P(threshold) < 0.001 for inclusion in polygenic risk score calculations.

		Model 1[c]	Model 2[c]
Population with schizophrenia			
PRS-SCZ	As scale[a]	0.91 (0.87–0.95), p < 0.001	0.91 (0.86–0.95), p < 0.001
	Highest decile[b]	0.73 (0.59–0.89), p = 0.002	0.72 (0.59–0.88), p = 0.001
PRS-DEP	As scale[a]	0.99 (0.86–1.13), p = 0.87	1.00 (0.87–1.15), p = 0.97
	Highest decile[b]	1.13 (0.93–1.37), p = 0.23	1.14 (0.94–1.38), p = 0.19
PRS-BIP	As scale[a]	1.00 (0.93–1.08), p = 0.95	1.04 (0.96–1.12), p = 0.36
	Highest decile[b]	1.05 (0.85–1.29), p = 0.65	1.08 (0.88–1.32), p = 0.48
Population with unipolar depression			
PRS-SCZ	As scale[a]	1.01 (1.00–1.02), p = 0.15	1.01 (1.00–1.02), p = 0.06
	Highest decile[b]	0.91 (0.87–0.97), p = 0.001	0.92 (0.87–0.97), p = 0.002
PRS-DEP	As scale[a]	0.99 (0.96–1.02), p = 0.51	0.99 (0.96–1.02), p = 0.52
	Highest decile[b]	0.98 (0.93–1.03), p = 0.37	0.98 (0.94–1.03), p = 0.41
PRS-BIP	As scale[a]	0.98 (0.96–1.00), p = 0.01	0.98 (0.96–0.99), p = 0.007
	Highest decile[b]	0.98 (0.93–1.03), p = 0.41	0.99 (0.94–1.04), p = 0.58
Population with bipolar disorder			
PRS-SCZ	As scale[a]	1.02 (0.99–1.06), p = 0.25	1.03 (0.99–1.07), p = 0.10
	Highest decile[b]	1.06 (0.87–1.29), p = 0.57	1.06 (0.87–1.29), p = 0.55
PRS-DEP	As scale[a]	0.94 (0.82–1.07), p = 0.37	0.94 (0.82–1.07), p = 0.33
	Highest decile[b]	0.96 (0.77–1.19), p = 0.71	0.96 (0.77–1.19), p = 0.70
PRS-BIP	As scale[a]	0.91 (0.84–0.98), p = 0.01	0.90 (0.83–0.97), p = 0.006
	Highest decile[b]	0.99 (0.83–1.18), p = 0.89	0.98 (0.82–1.17), p = 0.84
Control population			
PRS-SCZ	As scale[a]	1.00 (0.98–1.02), p = 0.85	1.00 (0.99–1.02), p = 0.65
	Highest decile[b]	1.00 (0.92–1.10), p = 0.94	1.01 (0.92–1.10), p = 0.85
PRS-DEP	As scale[a]	0.95 (0.90–1.00), p = 0.04	0.95 (0.90–1.00), p = 0.05
	Highest decile[b]	0.94 (0.86–1.03), p = 0.18	0.94 (0.86–1.03), p = 0.18
PRS-BIP	As scale[a]	0.96 (0.93–0.99), p = 0.007	0.96 (0.93–0.99), p = 0.009
	Highest decile[b]	0.95 (0.87–1.03), p = 0.24	0.95 (0.87–1.03), p = 0.19

PRS: Polygenic risk score. PRS-SCZ/DEP/BIP: PRS for schizophrenia, unipolar depression, or bipolar disorder, respectively. IRR: Incidence rate ratio. Parentheses are 95% confidence intervals. All models adjusted for the top four ancestral principal components.

[a] IRR reflects a one-point increase in PRS.

[b] Highest decile of PRS versus remaining nine deciles.

[c] In model 1, each PRS is entered individually. In model 2, each PRS is adjusted for the two other PRS's of the same kind – i.e. all "as scale" estimates adjusted for other "as scale" PRS's, and all "highest decile" estimated adjusted for other "highest decile" PRS's.

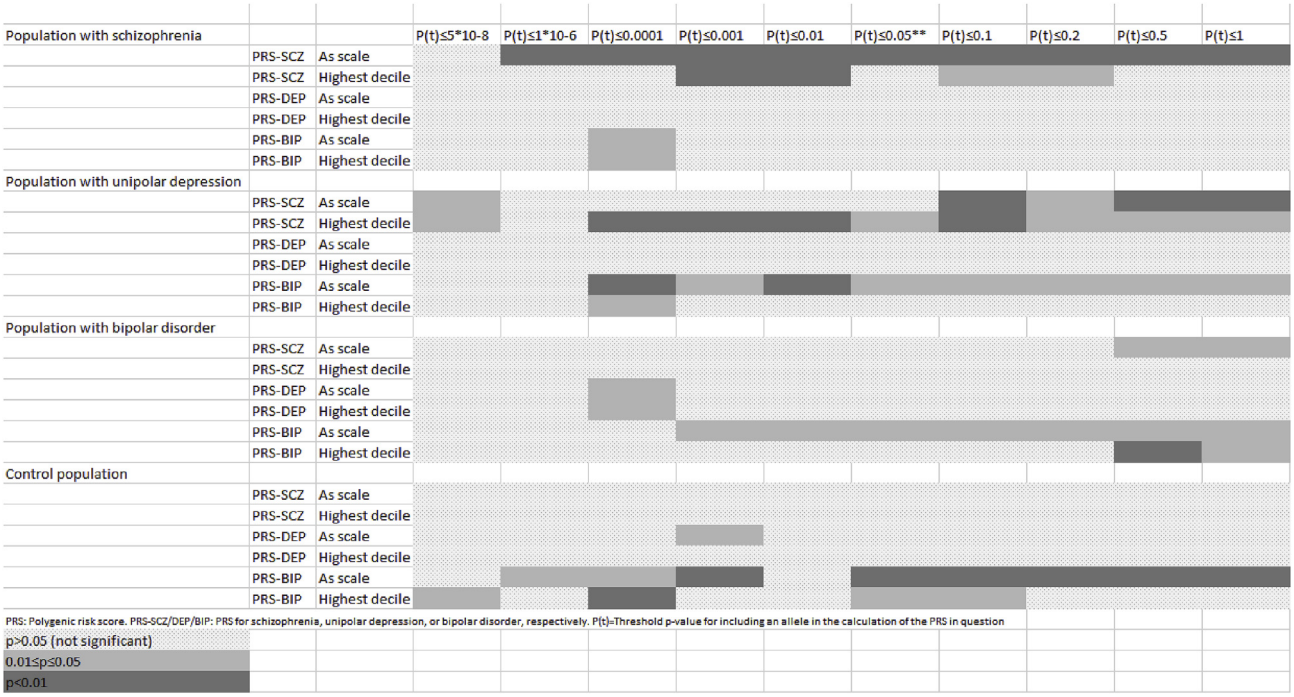

Fig. 1. P-values for the associations between polygenic risk scores and singleness using different p(t) for including alleles in the calculation of polygenic risk scores.

3.1.3. Population with bipolar disorder

Among patients with bipolar disorder, only the polygenic risk score for bipolar disorder was associated with a reduction in days in cohabiting relationships, and only when the PRS was included as a linear variable. The PRS for schizophrenia or unipolar depression were not associated with days in cohabiting relationships (all p > 0.25). Fig. 1 indicates that these results were stable across different p(t)-values, although the polygenic risk score for schizophrenia became a significant

predictor of singleness in this population at $p(t) \leq 0.5$ and $p(t) \leq 1$. McFadden's pseudo R-squared ranged between 1 and 2%. There were virtually no differences between model 1 and model 2 (in which PRS's were mutually adjusted).

3.1.4. Control population

Among controls, the polygenic risk score for bipolar disorder was associated with fewer days in cohabiting relationships. The PRS for unipolar depression showed a tendency in the same direction, although this was only statistically significant in one of the four parametrizations and with $0.08 < p < 0.09$ for two of the other parametrizations. The PRS for schizophrenia was not associated with a reduction in days in cohabiting relationships in the non-psychiatric controls (all $p > 0.27$). Fig. 1 indicates that these results were stable across different p(t)-values. McFadden's pseudo R-squared was generally around 1%. There were virtually no differences between model 1 and model 2 (in which PRS's were mutually adjusted).

4. Discussion

4.1. Main findings

The present study investigated whether genetic factors are associated with singleness in schizophrenia, bipolar disorder, unipolar depression and controls. We examined if the polygenic risk score for schizophrenia, bipolar disorder and unipolar depression influence time in couple relationships. Higher polygenic risk score for schizophrenia was associated with fewer days in couple relationships among people with schizophrenia or unipolar depression. Higher PRS for bipolar disorder was also associated with fewer days in couple relationships among patients with unipolar depression or bipolar disorder, as well as controls. The PRS for depression showed tendencies for an association with fewer days in cohabiting relationships but only among people with bipolar disorder. We also found markedly higher rates of singleness in patients with schizophrenia than in the other three populations.

4.2. PRS and singleness in cases with schizophrenia and controls

The rather weak, but statistically significant, association between PRS for schizophrenia and singleness in people with schizophrenia may primarily be due to disease-specific factors. This would be consistent with evidence that poor premorbid social functioning constitutes a marker of illness vulnerability in the schizophrenia spectrum (Schiffman et al., 2004; Tsuji et al., 2013; Zammit et al., 2004). and findings suggesting that poor premorbid social functioning is a prognostic indicator of a continuous course of illness in first-episode patients (Bertelsen et al., 2009). Polygenic risk scores for schizophrenia might affect subclinical traits related to personality in the population, possibly including introversion (Kendler, 2016). For instance, a cohort study in 9912 UK adolescents found that PRS for schizophrenia did not predict psychotic symptoms in adolescents but was associated with higher self-rated scores on negative symptom scales and on anxiety (Jones et al., 2016).

Higher polygenic risk score for bipolar disorder was associated with fewer days in couple relationships in patients with unipolar depression or bipolar disorder and controls. This finding may be interpreted in the light of recent findings based on samples of from 2654 to 6111 young adults from the UK where genetic risk for bipolar disorder did not appear to manifest in childhood to the same extent than genetic risk for schizophrenia has been reported to do (Mistry et al., 2019). However, it is still possible that genetic risk for bipolar disorder could affect subclinical traits including personality traits in populations that could, in turn, be associated with singleness. It is uncertain, whether the effects that we observed in affective disorder patients and in controls are mediated primarily by direct effects of biology or by an interplay between personality traits and environmental factors that we did not have data on. But we cannot rule out that biological pleiotropy could have played a role. An indicator of biological pleiotropy has previously been found to exist between personality traits like neuroticism and mental health (Gale et al., 2016).

4.3. PRS and singleness in cases with mood disorders

Higher polygenic risk score for schizophrenia was linearly associated with fewer days in couple relationships among patients with unipolar depression. This could also represent biological pleiotropy where PRS for schizophrenia contributes independently to multiple phenotypes. There is a conjecture of findings from the Avon Longitudinal Study where our findings add new evidence. For instance, a study found that among children aged 7–9 years, PRS for schizophrenia showed associations with lower performance intelligence quotient, poorer social understanding and worse language intelligibility and fluency, more irritability and more headstrong behavior (Riglin et al., 2017). Another study found that depression with a relatively early age at onset was associated with genetic liability to schizophrenia (Power et al., 2017). It is possible that PRS for schizophrenia explains a proportion of phenotypic variance (related to stability, for instance) that could correlate with factors that hinder long-term engaging in couple relationships.

4.4. Variance explained

While Poisson regression does not provide an R-squared value directly comparable to that produced in ordinary least squares regression, we estimated for each model the McFadden's pseudo R-squared. While interpretation of this value is not exactly the same as proportion of variance explained, it is similar. McFadden's pseudo R-squared was low for analyses on the population with unipolar depression, and around 1–2% in the remaining three populations. This certainly indicates that many things are more important than psychiatric genetic risk scores in predicting singleness. However, it also indicates that such genetics is important enough to have potential effects into people's social lives.

4.5. Strengths and limitations

Genotyping was done on all individuals with schizophrenia and bipolar disorder, and a random subsample of individuals with unipolar depression. Further, the DNA was extracted from dried neonatal bloodspots, and as such was obtained before diagnosis of the psychiatric disorder in question. Population-based incident sample are less selected for chronicity and less depleted for early deaths, as cases with good prognosis or short survival time are as likely to be included as cases with long and chronic duration of illness (Meier et al., 2016). Consequently, the risk of selection bias is almost non-existent. Furthermore, we were able to rely on register information which is available for the entire sample due to the unselected, nationwide Danish registers. There was thus no missing information on any variables, which would usually be the case when relying on self-reported information.

The use of register-based information, however, also introduces some limitations. Since the diagnoses were obtained from treatment registers, they did not contain information on type and severity of symptoms. Only patients with the three psychiatric disorders diagnosed in the secondary sector were included in the study populations. While probably unproblematic for schizophrenia and bipolar disorder, many patients with unipolar depression are likely to be seen exclusively in the primary sector, i.e. by their general practitioner. Consequently, our results for the population with unipolar depression may only be valid for the more severe end of the spectrum.

In the present analysis, we use only a single outcome measure, namely that of singleness. As such, it is not directly possible to gauge whether our results are specific to this outcome, or if they rather reflect overall risk of social disintegration. Future studies should test this

hypothesis, e.g. by including outcomes such as time in full occupation.

We tested associations across types of PRS and psychiatric disorders. This may be seen as a strength as it provides a more detailed overview. However, there is a limitation in how to draw inferences from analyses based on multiple testing. As both the disorders and the polygenic risk scores are likely to be correlated, we did not consider adjusting for multiple testing (e.g. Bonferroni correction), as these are only useful if the statistical tests conducted are more or less independent. Consequently, introducing such corrections would lead to an unacceptable increase in the risk of type II errors, without really giving estimates that are adequate in terms of the risk of type I errors. However, as many of our statistically significant findings have $0.01 < p < 0.05$, it may be worthwhile exercising caution in interpretation of results.

In summary, our findings implicate high genetic loading for schizophrenia as a predisposing factor to singleness in patients with schizophrenia, unipolar depression and bipolar disorder. Patients with schizophrenia had markedly fewer days/year in couple relationships: 64 (95% CI; 61–69) than patients with unipolar depression: 119 (95% CI; 117–121), bipolar disorder: 103 (95% CI 97–110), and controls 136 (95% CI 133–139).

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Conflicts of interest

All authors declare that we have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.09.013.

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