SUPPLEMENT

Not all bipolar disorder outcomes are created equal: occupational dysfunction and hospital admissions associate with different polygenic profiles

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Supplementary methods

Phenotype description in SWEBIC

The longitudinal integrated database for health insurance and labour market studies (LISA) database started in 1990 and includes all individuals 16 years of age and older who were registered in Sweden as of December 31 for each year.[1] We have included employment status between 1993-2015 according to the variables called "SyssStat", "SysstatJ" and "Sysstat11" in LISA. These data are built on reports in October and November every year regarding occupational status, thus we have one registration per year for each individual.

The LISA database also includes information about number of days absent from work due to illness during the years 1993-2015. We used the net number of days absent from work due to illness ("full sickness days"; e.g., a subject with 50% sick leave for 20 days will be recorded as 10 days of sick leave) (LISA variable named "SjukP_Ndag").[1] We also included information about early retirement, defined as someone who had received "disability pension", "sickness allowance", "sickness compensation" or "activity benefit" (LISA variable named "ForTid"). For each year, "long-term sick leave or early retirement" was defined as having over 60 full sickness days or received any payments for early retirement.

We used so called MVO codes to define psychiatric hospital admissions included in the Swedish national patient registry (MVO codes 901 and 931).

We included sensitivity analyses correcting for age of onset. We defined age of onset as age at first symptoms reported in the quality registry BipoläR. The included question had five age options: 1) -7 years, 2) 8-11 years, 3) 12-17 years, 4) 18-24 years, and 5) >24 years. These responses were dichotomised to age at first symptom before or after age 24 In total 1,621 patients reported first symptoms before age 24 while 852 patients after age 24.

Table S1. Regression association results between PGS and the included phenotypes including results when correcting for age at first symptoms defined as before or after age 24.

Phenotype/PGS	OR (95% CI)	P^a	OR (95% CI)	$P_{corrAOO}{}^b$
Without employment	(N=4,139)		*(N=2,111)*	
Bipolar disorder-PGS	0.99 (0.94-1.06)	0.85	0.95 (0.87-1.04)	0.25
Schizophrenia-PGS	1.16 (1.09-1.24)	**4.1E-06**	1.14 (1.04-1.24)	**0.0047**
Depression-PGS	1.17 (1.1-1.24)	**1.9E-07**	1.10 (1.01-1.20)	**0.022**
ADHD-PGS	1.13 (1.07-1.2)	**3.9E-05**	1.17 (1.08-1.27)	**1.0E-04**
Educational attainment-PGS	0.83 (0.78-0.88)	**7.6E-11**	0.79 (0.73-0.86)	**9.8E-09**
AUDIT-PGS	1.01 (0.95-1.06)	0.83	1.01 (0.94-1.1)	0.75
Long-term sick leave	(N=4,139)		(N=2,111)	
Bipolar disorder-PGS	0.95 (0.89-1.01)	0.093	0.94 (0.86-1.02)	0.13
Schizophrenia-PGS	1.08 (1.02-1.16)	0.012	1.03 (0.95-1.13)	0.48
Depression-PGS	1.20 (1.14-1.28)	**3.0E-10**	1.16 (1.07-1.26)	**3.0E-04**
ADHD-PGS	1.12 (1.06-1.19)	**6.4E-05**	1.15 (1.06-1.24)	**6.3E-04**
Educational attainment-PGS	0.85 (0.8-0.89)	**3.0E-09**	0.83 (0.76-0.89)	**2.0E-06**
AUDIT-PGS	0.99 (0.93-1.04)	0.63	0.95 (0.88-1.02)	0.17
Hospitalizations	(N=4,782)		*(N=2,473)*	
Bipolar disorder-PGS	1.14 (1.08-1.21)	**2.4E-06**	1.18 (1.09-1.27)	**3.4E-05**
Schizophrenia-PGS	1.23 (1.16-1.3)	**6.5E-12**	1.22 (1.12-1.32)	**1.7E-06**
Depression-PGS	1.07 (1.01-1.12)	0.019	1.01 (0.94-1.09)	0.81
ADHD-PGS	0.99 (0.94-1.05)	0.78	0.98 (0.91-1.06)	0.63
Educational attainment-PGS	1.0 (0.95-1.05)	0.94	0.99 (0.92-1.06)	0.78
AUDIT-PGS	1.0 (0.95-1.05)	0.88	0.98 (0.91-1.05)	0.52

AOO=Age of onset defined as age at first symptom before/after age 24. [a]Bold indicates signficant results in the main analyses after correction for multiple testing $P<0.0028$. [b]Bold indicates $P<0.05$ in sensitivity analyses correcting for AOO.

Table S2. Results from sensitivity analyses between PGS and phenotype age-specific intensities, including age at first symptom as covariate.

	Intensity before age 40[a]				*Intensity after age 40*[b]			
	OR(95%CI)	***P*[c]**	***OR(95%CI)*$_{corr}$**	***P*$_{corr}$[d]**	**OR(95%CI)**	***P*[c]**	***OR(95% CI)*$_{corr}$**	***P*$_{corr}$[d]**
Without employment	Age 25-39 (N=1,649)		Age 25-39 (N=873)		Age 40-65 (N=2,999)		Age 40-65 (N=1,498)	
Bipolar disorder-PGS	0.97 (0.88-1.06)	0.50	0.96 (0.85-1.10)	0.58	1.01 (0.94-1.08)	0.83	0.95 (0.86-1.05)	0.33
Schizophrenia-PGS	1.11 (1.00-1.23)	**0.043**	1.12 (0.97-1.29)	0.13	1.19 (1.10-1.28)	**6.9E-06**	1.13 (1.02-1.26)	**0.019**
Depression-PGS	1.07 (0.98-1.18)	0.13	1.05 (0.92-1.20)	0.46	1.21 (1.13-1.30)	**3.5E-08**	1.12 (1.01-1.23)	**0.026**
ADHD-PGS	1.13 (1.03-1.24)	**0.012**	1.18 (1.04-1.33)	**0.011**	1.14 (1.06-1.22)	**2.6E-04**	1.19 (1.08-1.31)	**6.0E-04**
Educational attainment-PGS	0.86 (0.78-0.94)	**6.5E-04**	0.82 (0.72-0.93)	**0.0014**	0.80 (0.75-0.86)	**7.1E-11**	0.77 (0.70-0.85)	**1.7E-07**
AUDIT-PGS	0.98 (0.90-1.08)	0.70	1.06 (0.93-1.20)	0.41	1.01 (0.95-1.08)	0.74	1.01 (0.93-1.11)	0.77
Long-term sick leave	Age 25-39 (N=1,649)		Age 25-39 (N=873)		Age 40-65 (N=2,999)		Age 40-65 (N=1,498)	
Bipolar disorder-PGS	0.92 (0.83-1.01)	0.090	0.99 (0.86-1.13)	0.84	0.97 (0.90-1.04)	0.38	0.90 (0.81-1.00)	0.051
Schizophrenia-PGS	1.04 (0.94-1.15)	0.46	1.09 (0.95-1.26)	0.22	1.12 (1.04-1.21)	**0.0027**	1.02 (0.91-1.13)	0.74
Depression-PGS	1.13 (1.02-1.24)	**0.015**	1.14 (1.00-1.31)	0.055	1.21 (1.13-1.30)	**4.1E-08**	1.12 (1.02-1.24)	**0.024**
ADHD-PGS	1.11 (1.01-1.21)	**0.034**	1.11 (0.98-1.26)	0.10	1.11 (1.04-1.19)	**0.0023**	1.12 (1.02-1.23)	**0.022**
Educational attainment-PGS	0.85 (0.78-0.93)	**4.7E-04**	0.79 (0.70-0.90)	**2.1E-04**	0.84 (0.78-0.90)	**3.1E-07**	0.82 (0.75-0.91)	**1.1E-04**
AUDIT-PGS	0.93 (0.85-1.02)	0.14	0.93 (0.82-1.06)	0.29	1.00 (0.93-1.06)	0.89	0.95 (0.87-1.04)	0.29
Hospitalizations	Age 15-39 (N=4,180)		Age 15-39 (N=2,189)		Age 40-70 (N=3,213)		Age 40-70 (N=1,606)	
Bipolar disorder-PGS	1.20 (1.13-1.27)	**3.2E-09**	1.26 (1.16-1.37)	**9.6E-08**	1.00 (0.94-1.07)	0.96	1.03 (0.94-1.14)	0.50
Schizophrenia-PGS	1.23 (1.15-1.31)	**2.9E-10**	1.23 (1.13-1.35)	**3.8E-06**	1.16 (1.08-1.25)	**4.1E-05**	1.14 (1.03-1.25)	**0.012**
Depression-PGS	1.03 (0.98-1.10)	0.25	0.97 (0.90-1.06)	0.53	1.12 (1.05-1.19)	**6.3E-04**	1.08 (0.99-1.18)	0.099
ADHD-PGS	0.95 (0.90-1.01)	0.097	0.96 (0.89-1.04)	0.35	1.00 (0.94-1.07)	0.98	0.96 (0.88-1.06)	0.44
Educational attainment-PGS	1.12 (1.06-1.19)	**4.9E-05**	1.14 (1.06-1.24)	**6.8E-04**	0.89 (0.84-0.95)	**4.3E-04**	0.89 (0.82-0.98)	**0.013**
AUDIT-PGS	1.01 (0.96-1.07)	0.70	1.01 (0.94-1.10)	0.74	1.02 (0.96-1.09)	0.50	0.99 (0.91-1.08)	0.89

Bold indicates uncorrected *P*-values <0.05. [a]Age 25-39 for employment and sick leave/ Age 15-39 for hospitalizations. [b]Age 40-65 for employment and sick leave / Age 40-70 for hospitalizations. [c]*P*-values for main analyses of intensities during the time before and after age 40. [d]P_{corr}=including age at first symptom (before/after age 24) as covariate in regression analyses.

REFERENCES

1. Ludvigsson JF, Svedberg P, Olen O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34(4):423-37.