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Mental health and use of psychotropic prescription drugs in adult patients with primary immune thrombocytopenia: a nationwide population-based cohort study

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SUPPLEMENTARY METHODS AND MATERIALS

SUPPLEMENTARY METHODS

Data extraction and outcomes

The Danish nationwide health registries contains valid and continuously updated data with full follow-up.[1-4] Hospitalizations have been recorded since 1977 in the Danish National Patient Registry (DNPR), and includes data from outpatient clinics and emergency rooms since 1994.[2,5] The Danish Psychiatric Central Research Register (DPCRR) hold valid information on psychiatric admissions and diagnoses since 1970, while the Danish Civil Registration System (DCRS) contains complete data on sex, dates of birth and death, and migration.[3,6,7] Since 1995, the Danish National Prescription Registry (NPR) have recorded all redeemed prescriptions, and thereby contains highly valid data on dispensed prescriptions including detailed Anatomic Therapeutic Codes (ATC) codes, amounts of drugs, and date of dispensing, making it a powerful pharmacoepidemiological tool.[1,8] All individuals can be tracked through a unique and permanent identification number, allowing cross-registry individual-level-linkage.[7]

We used the first registration of the designated International Classification of Diseases (ICD) code (D69.3) as index date, similar to a previous study by our group.[9] Comparators were allotted the same index date. We categorized patients as secondary ITP if they were registered with at least one predefined qualifying diagnosis any time before or up to 30 days after the first registration of ITP using a previously applied approach.[9,10]

We followed the patients and comparators to the first of: hospital registered mental health event including fatigue, emigration, death, or end of study period (31st of December 2016). Individuals with a given prevalent mental health event at index date were excluded from incidence analysis, but remained in follow-up for the other types of mental health events. We stratified analyses according to patients and comparators age (18-59, 60+ years) and sex, as well as period of index date (1997-2006, 2007-2016).

The mental health event outcomes were identified in the DNPR using the relevant ICD registrations (supplementary table S1). Each type of first registered mental health event including fatigue occurring after index date was categorized as incident, and registrations before this date were prevalent.

We categorized comorbidity into 12 categories defined by the 2011 updated Charlson Comorbidity Index (CCI)[11]: heart failure, dementia, chronic pulmonary disease, connective tissue disease, diabetes with chronic complications, hemiplegia, any tumor/lymphoma/leukemia, mild liver disease, moderate-severe liver disease, renal disease, AIDS/HIV, and metastatic solid tumor (supplementary table S2). We also included diagnoses of substance abuse defined solely on designated registrations in the DNPR (supplementary table

S2). This approach of classifying individual level comorbidity in longitudinal studies through the DNPR has previously been proven valid.[12]

Many psychiatric disorders are treated in the primary health care sector by general practitioners without hospital referral, and thereby not captured in the nationwide patient registry which is hospital-based.[5] Therefore, we also included data from the entire Danish health sector of reimbursed prescriptions of psychotropic drugs as a proxy measure of mental health burden.
To align the availability of the different registry-data and to introduce a full 24-months run-in period of the prescription data, we only investigated individuals diagnosed from January 1st 1997 and onwards.

Statistics

We estimated unadjusted and adjusted subdistribution hazard ratios through Fine-Gray proportional subdistribution hazard regressions treating death and emigration as competing events.[13-15] Time-splitted analyses estimating overall, 1st year, 2-5th year, and 6-10th year after the index date were performed for both Cox and Fine-Gray regressions. We estimated the absolute incident risk of mental health event including fatigue by 1-year, 5-year, 10-year and end of study cumulative incidences for both patients with ITP and comparators.[15] We used the Altman-Bland method to test for interaction between estimates derived from subgroups, with a p-value <0.05 considered significant.[16]
Monthly incidence-rates (IR) of psychotropic drugs were estimated per 100-personyears (PY) for each category up to 24 months before and 24 months after diagnosis of ITP, using the first prescription within each category, and demanding that individuals had full follow-up in each of the months investigated. Incidence-rate-ratios (IRR) and incidence-rate-differences (IRD) were estimated to measure both relative and absolute differences in number of prescriptions between patients and comparators. Since individuals could receive multiple prescriptions for different psychotropic drugs over time, we also estimated the prevalence proportions of patients and comparators receiving a minimum of one prescription within each category of psychotropic drugs in a year with full follow-up. The analyses of temporal relation of drug use prior to and after diagnosis of ITP required a full 5-year run-in period, and therefore only included individuals diagnosed with ITP from January 1st 2000 and onwards. We have used similar approaches in previous studies.[9,17]

Sensitivity analysis

We performed two sensitivity analyses where we repeated the csHR estimates. The first one excluding individuals with no history of mental health events including fatigue, and the second excluding individuals with prior use of any psychotropic drug up to 24 months before diagnosis of ITP. We also sampled comparators based on hospital contacts within the medical specialties: dermatology, oncology, rheumatology and pulmonology. This was done to compare the use of psychotropic drugs among comparators affiliated with other departments typically following individuals burdened with chronic diseases and comorbidity.

All data-management and statistical analyses were performed using Stata 18.0 (StataCorp, 4905 Midtown Dr., College Station, TX 77845, USA).

SUPPLEMENTARY TABLES

Supplementary table S1. List of ICD-codes defining mental health events including fatigue and psychotropic drugs

MENTAL HEALTH EVENTS INCLUDING FATIGUE	
SCHIZOPHRENIA & PSYCHOSES	
ICD-10 codes	*PSYCHOSES* F105, F115, F125, F135, F145, F155, F165, F185, F195, F24.x *SCHIZOPHRENIA* F200, F201-F203, F205, F206, F208, F209, F21.x *OTHER PSYCHOSES* F22.x, F23.x, F25.x, F28.x, F29.x
DEPRESSION	
ICD-10 codes	F204, F32, F33, F3411
MANIA & BIPOLAR AFFECTIVE DISORDER	
ICD-10 codes	F30, F31
ANXIETY & OBSESSIVE COMPULSIVE DISORDER (OCD)	
ICD-10 codes	*ANXIETY* F40, F41 *OCD* F42
FATIGUE	
ICD-10 codes	R53
ATC-codes for psychotropic drug exposure	
NAME	*ATC-code*
	Antidepressants (N06A) Antipsychotics (N05A) Benzodiazepines (N03AE, N05BA, N05CD, N05CF) Opioids (N02A)

Supplementary table S1. ICD-10 – and ATC-codes used to identify mental health events including fatigue and psychotropic drugs. We divided mental health events into five subgroups: schizophrenia and psychoses, depression, mania and bipolarity, anxiety and obsessive-compulsive disorder (OCD), and fatigue. We divided drugs into four subgroups: antidepressants, antipsychotics, benzodiazepines, and opioids. For both the mental health events and psychotropic drug groups, an accumulated group including the first of any of the aforementioned respective subgroups was also made.
Abbreviations: ICD = International Classification of Disease, ATC = Anatomic Therapeutic Classification

Supplementary table S2. List of included ICD-codes defining comorbidity

Condition	ICD-8	ICD-10
***Alcohol consumption**	29119, 30319, 30320, 30328, 30329, 57109, 57110	F101, F102, G312A-E, G621, K70, K860, T519, Z714
***Drug abuse / intoxication**	96790	F110-F114, F117-F119, F120-F122, F127-F129, F130-F134, F137-F139, F140-F143, F147-F149, F150-F153, F157-F159, F160-F162, F167-F169, F180-F182, F186-F189, F190-F194, F196-F199, F550, T40x, T42x, T43x, Z864
Congestive heart failure	427.0, 427.09, 427.1, 427.10, 427.11, 427.19, 428, 428.99, 782.4, 782.49	I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429, I43, I50, P290
Dementia	290.09, 290.10, 290.11, 290.18, 290.19, 293.09	F00, F01, F02, F03, F051, G30, G311
Chronic pulmonary disease	490, 491, 492, 493, 515, 516, 517, 518	J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J701, J703, J841, J920, J961, J982, J983
Connective tissue disease	135, 135.99, 446, 712, 716, 734	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Diabetes with chronic complications	249.01, 249.02, 249.03, 249.04, 249.05, 249.08, 250.01, 250.02, 250.03, 250.04, 250.05, 250.08	E102, E103, E104, E105, E106, E107, E108, E112, E113, E114, E115, E116, E117, E118, E122, E123, E124, E125, E126, E127, E128, E132, E133, E134, E135, E136, E137, E138, E142, E143, E144, E145, E146, E147, E148
Hemiplegia	343.0, 344	G114, G801, G802, G81, G82, G830, G831, G832, G833, G834, G839
Any tumor, lymphoma, or leukemia	140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 200, 201, 202, 203, 204, 205, 206, 207, 27599	C00, C01, C02, C03, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C27, C28, C29, C30, C31, C32, C33, C34, C35, C36, C37, C38, C39, C40, C41, C42, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C59, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95, C96
Mild liver disease	571, 573.01, 57304	B18, K713, K714, K715, K717, K73, K74, K760, K7602, K7603, K7604, K7608, K7609, Z944
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 571.10, 456.00, 456.01, 456.09, 573.00	B150, B160, B162, B190, I85, I864, I982, K704, K711, K72, K765, K766, K767
Renal disease	403, 404, 580, 581, 582, 583, 584, 590.09, 593.19, 753.1, 753.1, 753.1, 792, 997.70	I12, I13N00, N01, N02, N03, N04, N05, N07, N11, N14, N17, N18, N19, N250, Q61, Z940, Z992
AIDS/HIV	07983	B20, B21, B22, B23, B24
Metastatic solid tumor	196, 197, 198, 199	C77, C78, C79, C80

Supplementary table S2. ICD-codes applied to assess prevalent comorbidity among patients and comparators. Twelve groups were defined by the 2011 updated CCI[11], while two categories (alcohol consumption and drug abuse/intoxication marked with *) were defined through ICD-codes. Comorbidity-score was divided in 0, 1-2 or >2 points. Covariates were included as dichotomous variables in the regressions.[18]
Abbreviations: AIDS = acquired immune deficiency syndrome, HIV = human immunodeficiency virus

Supplementary table S3. Cumulative incidence proportions for mental health events including fatigue in patients with primary ITP and general population comparators

Name	**Primary ITP (%) (95% CI)**	**Comparators (%) (95% CI)**
END OF 1st YEAR		
Scizophrenia / Psychosis	0.22 (0.11-0.42)	0.07 (0.06-0.09)
Depression	1.19 (0.87-1.60)	0.34 (0.31-0.37)
Mania / Bipolarity	0.11 (0.04-0.27)	0.03 (0.02-0.04)
Anxiety / OCD	0.28 (0.14-0.50)	0.13 (0.11-0.15)
Fatigue	0.86 (0.60-1.21)	0.20 (0.18-0.23)
Any mental health event	2.34 (1.87-2.89)	0.66 (0.62-0.70)
END OF 5th YEAR		
Scizophrenia / Psychosis	0.49 (0.29-0.78)	0.35 (0.32-0.38)
Depression	2.50 (1.99-3.09)	1.85 (1.77-1.93)
Mania / Bipolarity	0.21 (0.10-0.43)	0.17 (0.15-0.19)
Anxiety / OCD	1.31 (0.96-1.77)	0.69 (0.65-0.74)
Fatigue	2.46 (1.96-3.05)	1.22 (1.16-1.28)
Any mental health event	5.63 (4.85-6.49)	3.53 (3.43-3.64)
END OF 10th YEAR		
Scizophrenia / Psychosis	0.73 (0.46-1.11)	0.61 (0.56-0.66)
Depression	4.17 (3.43-5.01)	3.55 (3.43-3.67)
Mania / Bipolarity	0.25 (0.12-0.49)	0.34 (0.31-0.38)
Anxiety / OCD	2.52 (1.95-3.21)	1.37 (1.29-1.44)
Fatigue	4.31 (3.56-5.16)	2.53 (2.43-2.63)
Any mental health event	9.45 (8.32-10.66)	6.81 (6.65-6.98)
END OF STUDY TIME		
Scizophrenia / Psychosis	0.86 (0.52-1.36)	0.99 (0.89-1.11)
Depression	5.76 (4.66-7.03)	5.76 (5.51-6.03)
Mania / Bipolarity	0.37 (0.16-0.77)	0.63 (0.54-0.72)
Anxiety / OCD	3.76 (2.78-4.94)	2.86 (2.41-3.36)
Fatigue	6.15 (4.80-7.73)	5.64 (5.34-5.95)
Any mental health event	13.50 (11.56-15.58)	12.61 (12.02-13.22)
ANY MENTAL HEALTH EVENT		

END OF 1st YEAR		
Male	2.06 (1.45-2.84)	0.58 (0.52-0.64)
Female	2.60 (1.94-3.41)	0.73 (0.67-0.80)
18-59years	1.91 (1.34-2.64)	0.53 (0.48-0.59)
60+ years	2.78 (2.08-3.65)	0.79 (0.73-0.86)
1997-2006	1.66 (1.09-2.44)	0.54 (0.48-0.60)
2007-2016	2.79 (2.14-3.58)	0.75 (0.69-0.81)
END OF 5th YEAR		
Male	5.35 (4.25-6.63)	3.33 (3.18-3.48)
Female	5.88 (4.81-7.10)	3.71 (3.57-3.86)
18-59years	4.87 (3.87-6.04)	2.66 (2.54-2.80)
60+ years	6.41 (5.25-7.73)	4.42 (4.26-4.59)
1997-2006	3.61 (2.72-4.69)	2.78 (2.65-2.92)
2007-2016	7.40 (6.17-8.78)	4.24 (4.08-4.41)
END OF 10th YEAR		
Male	8.93 (7.33-10.71)	6.34 (6.10-6.57)
Female	9.89 (8.35-11.58)	7.21 (6.98-7.44)
18-59years	8.59 (7.09-10.25)	5.29 (5.09-5.49)
60+ years	10.43 (8.76-12.25)	8.48 (8.22-8.75)
1997-2006	7.15 (5.88-8.59)	5.76 (5.57-5.96)
2007-2016	N/A	N/A
END OF STUDY TIME		
Male	11.45 (8.50-14.88)	11.62 (10.97-12.30)
Female	15.13 (12.59-17.88)	13.34 (12.58-14.12)
18-59years	13.41 (10.93-16.15)	11.15 (10.29-12.05)
60+ years	14.04 (10.68-17.85)	14.59 (13.95-15.24)
1997-2006	11.17 (9.17-13.39)	11.58 (10.98-12.19)
2007-2016	11.55 (9.48-13.85)	8.49 (8.06-8.95)

Supplementary table S3. Cumulative incidences of mental health events including fatigue at 1, 5, 10 year, and end of study, after diagnosis of ITP (upper half). The cumulative incidences of any mental health event in groups by sex, age and calendar-years are also included (lower half). The competing events were death or emigration. The category 'any mental health event' included the first-ever hospital registration of schizophrenia/psychosis, depression, mania/bipolarity, anxiety/OCD or fatigue.
Abbreviations: ITP = immune thrombocytopenia, OCD = obsessive compulsive disorder, CI = confidence intervals

Supplementary table S4. Cox cause-specific hazard ratios (csHR) and Fine-Gray subdistribution hazard ratios (subHR) for risk of mental health events including fatigue in patients with primary ITP compared with the general population

Name	**Primary ITP (adjusted / unadjusted) (95% CI)**
ANY MENTAL HEALTH EVENT	
Overall	
Cox cause-specific HR	1.56 (1.38-1.76) / 1.60 (1.42-1.81)
Fine-Gray subHR	1.30 (1.15-1.47) / 1.40 (1.24-1.58)
1st year	
Cox cause-specific HR	3.57 (2.84-4.50) / 3.82 (3.04-4.80)
Fine-Gray subHR	3.30 (2.61-4.17) / 3.63 (2.89-4.57)
2-5th year	
Cox cause-specific HR	1.26 (1.02-1.55) / 1.31 (1.07-1.61)
Fine-Gray subHR	1.21 (0.98-1.48) / 1.27 (1.03-1.56)
6-10th year	
Cox cause-specific HR	1.45 (1.15-1.83) / 1.47 (1.17-1.86)
Fine-Gray subHR	1.40 (1.11-1.77) / 1.44 (1.14-1.81)
ANY MENTAL HEALTH EVENT BY SEX	
Male	
Cox cause-specific HR	1.57 (1.30-1.89) / 1.61 (1.34-1.95)
Fine-Gray subHR	1.23 (1.01-1.49) / 1.37 (1.13-1.66)
Female	
Cox cause-specific HR	1.57 (1.34-1.83) / 1.59 (1.36-1.86)
Fine-Gray subHR	1.36 (1.16-1.59) / 1.43 (1.22-1.67)
ANY MENTAL HEALTH EVENT BY AGE-GROUPS	
18-59 years	
Cox cause-specific HR	1.59 (1.34-1.90) / 1.72 (1.44-2.04)
Fine-Gray subHR	1.47 (1.23-1.76) / 1.62 (1.36-1.93)
60+ years	
Cox cause-specific HR	1.58 (1.33-1.86) / 1.63 (1.38-1.93)
Fine-Gray subHR	1.18 (0.99-1.39) / 1.26 (1.06-1.49)
ANY MENTAL HEALTH EVENT BY CALENDAR-YEARS	

1997-2006	
Cox cause-specific HR	1.28 (1.08-1.53) / 1.31 (1.10-1.56)
Fine-Gray subHR	1.06 (0.88-1.26) / 1.11 (0.93-1.32)
2007-2016	
Cox cause-specific HR	1.93 (1.63-2.27) / 1.99 (1.69-2.34)
Fine-Gray subHR	1.65 (1.40-1.96) / 1.80 (1.52-2.12)
ANY MENTAL HEALTH EVENT EXCLUDING FATIGUE	
Cox cause-specific HR	1.47 (1.27-1.70) / 1.54 (1.33-1.78)
Fine-Gray subHR	1.28 (1.10-1.49) / 1.35 (1.16-1.57)
SCHIZOPHRENIA / PSYCHOSIS	
Overall	
Cox cause-specific HR	1.29 (0.84-1.97) / 1.35 (0.88-2.07)
Fine-Gray subHR	1.13 (0.74-1.73) / 1.18 (0.77-1.81)
1st year	
Cox cause-specific HR	2.93 (1.41-6.08) / 3.20 (1.56-6.56)
Fine-Gray subHR	2.74 (1.32-5.72) / 3.02 (1.47-6.20)
2-5th year	
Cox cause-specific HR	1.08 (0.53-2.18) / 1.10 (0.55-2.22)
Fine-Gray subHR	1.03 (0.51-2.06) / 1.06 (0.53-2.15)
6-10th year	
Cox cause-specific HR	1.16 (0.48-2.82) / 1.19 (0.49-2.90)
Fine-Gray subHR	1.12 (0.46-2.75) / 1.16 (0.48-2.82)
DEPRESSION	
Overall	
Cox cause-specific HR	1.36 (1.14-1.63) / 1.40 (1.17-1.67)
Fine-Gray subHR	1.15 (0.96-1.38) / 1.21 (1.02-1.45)
1st year	
Cox cause-specific HR	3.53 (2.56-4.85) / 3.73 (2.72-5.11)
Fine-Gray subHR	3.26 (2.37-4.50) / 3.54 (2.58-4.86)
2-5th year	
Cox cause-specific HR	0.93 (0.67-1.29) / 0.96 (0.70-1.33)
Fine-Gray subHR	0.89 (0.64-1.23) / 0.93 (0.67-1.29)
6-10th year	

Cox cause-specific HR	1.22 (0.86-1.73) / 1.23 (0.87-1.74)
Fine-Gray subHR	1.18 (0.83-1.67) / 1.20 (0.85-1.70)
MANIA / BIPOLARITY	
Overall	
Cox cause-specific HR	0.93 (0.48-1.80) / 0.97 (0.50-1.88)
Fine-Gray subHR	0.82 (0.42-1.59) / 0.84 (0.43-1.63)
1st year	
Cox cause-specific HR	3.96 (1.42-11.04) / 3.68 (1.32-10.21)
Fine-Gray subHR	3.78 (1.39-10.32) / 3.47 (1.25-9.64)
2-5th year	
Cox cause-specific HR	0.73 (0.23-2.30) / 0.81 (0.26-2.54)
Fine-Gray subHR	0.69 (0.22-2.16) / 0.78 (0.25-2.45)
6-10th year	
Cox cause-specific HR	0.36 (0.05-2.57) / 0.36 (0.05-2.61)
Fine-Gray subHR	0.35 (0.05-2.54) / 0.35 (0.05-2.53)
ANXIETY / OCD	
Overall	
Cox cause-specific HR	1.81 (1.43-2.28) / 2.00 (1.58-2.51)
Fine-Gray subHR	1.58 (1.25-1.99) / 1.72 (1.37-2.17)
1st year	
Cox cause-specific HR	1.92 (1.01-3.65) / 2.26 (1.20-4.27)
Fine-Gray subHR	1.82 (0.96-3.44) / 2.14 (1.13-4.05)
2-5th year	
Cox cause-specific HR	1.89 (1.31-2.71) / 2.10 (1.46-3.01)
Fine-Gray subHR	1.83 (1.28-2.62) / 2.02 (1.41-2.90)
6-10th year	
Cox cause-specific HR	1.99 (1.32-3.01) / 2.20 (1.46-3.32)
Fine-Gray subHR	1.94 (1.28-2.94) / 2.14 (1.42-3.23)
FATIGUE	
Overall	
Cox cause-specific HR	1.86 (1.56-2.22) / 1.82 (1.53-2.17)
Fine-Gray subHR	1.40 (1.17-1.68) / 1.58 (1.32-1.89)
1st year	

Cox cause-specific HR	4.31 (2.97-6.27) / 4.60 (3.18-6.66)
Fine-Gray subHR	3.84 (2.63-5.60) / 4.35 (3.00-6.30)
2-5th year	
Cox cause-specific HR	1.81 (1.36-2.42) / 1.82 (1.36-2.43)
Fine-Gray subHR	1.71 (1.28-2.28) / 1.76 (1.32-2.35)
6-10th year	
Cox cause-specific HR	1.85 (1.33-2.57) / 1.76 (1.27-2.44)
Fine-Gray subHR	1.75 (1.25-2.43) / 1.72 (1.24-2.38)

Supplementary table S4. Risk of mental health events including fatigue in patients with primary ITP estimated as Cox cause-specific hazard ratios and Fine-Gray subdistribution hazard ratios, the latter taking death and emigration into account as competing events. We estimated both adjusted (left) and unadjusted estimates, as well as overall and time -splitted (1^{st}, $2\text{-}5^{th}$, $6\text{-}10^{th}$ year) risk estimates.
Abbreviations: ITP = immune thrombocytopenia, OCD = obsessive compulsive disorder, CI = confidence intervals

Supplementary table S5. Cox cause-specific hazard ratios for mental health events including fatigue using only individuals with no history of any mental health event and individuals with no prior use of any psychotropic drug <24 months before diagnosis of ITP

Cox cause-specific HR	Primary ITP NO PRIOR DISEASE (adjusted / unadjusted) (95% CI)	Primary ITP NO PRIOR DRUG <24M (adjusted / unadjusted) (95% CI)	Primary ITP MAIN (adjusted / unadjusted) (95% CI)
SCIZOPHRENIA / PSYCHOSIS			
Overall	1.42 (0.92-2.20) / 1.51 (0.97-2.32)	1.62 (0.91-2.89) / 1.71 (0.96-3.04)	1.29 (0.84-1.97) / 1.35 (0.88-2.07)
1st year	3.70 (1.77-7.73) / 4.06 (1.97-8.39)	5.07 (1.97-13.03) / 5.48 (2.17-13.84)	2.93 (1.41-6.08) / 3.20 (1.56-6.56)
5th year	1.12 (0.53-2.37) / 1.16 (0.55-2.47)	1.43 (0.53-3.87) / 1.42 (0.52-3.83)	1.08 (0.53-2.18) / 1.10 (0.55-2.22)
6-10th year	1.31 (0.54-3.20) / 1.33 (0.55-3.23)	1.48 (0.47-4.67) / 1.56 (0.49-4.91)	1.16 (0.48-2.82) / 1.19 (0.49-2.90)
DEPRESSION			
Overall	1.27 (1.05-1.53) / 1.30 (1.07-1.57)	1.21 (0.90-1.63) / 1.25 (0.93-1.68)	1.36 (1.14-1.63) / 1.40 (1.17-1.67)
1st year	2.90 (2.01-4.19) / 3.02 (2.10-4.35)	4.25 (2.44-7.39) / 4.42 (2.55-7.64)	3.53 (2.56-4.85) / 3.73 (2.72-5.11)
5th year	0.94 (0.67-1.31) / 0.98 (0.70-1.36)	0.76 (0.42-1.38) / 0.81 (0.44-1.46)	0.93 (0.67-1.29) / 0.96 (0.70-1.33)
6-10th year	1.19 (0.83-1.70) / 1.21 (0.85-1.72)	0.99 (0.56-1.75) / 1.01 (0.57-1.80)	1.22 (0.86-1.73) / 1.23 (0.87-1.74)
MANIA / BIPOLARITY			
Overall	0.86 (0.38-1.93) / 0.90 (0.40-2.02)	0.30 (0.04-2.13) / 0.33 (0.05-2.33)	0.93 (0.48-1.80) / 0.97 (0.50-1.88)
1st year	3.44 (0.81-14.51) / 3.20 (0.76-13.45)	7.44 (0.91-60.97) 6.76 (0.83-54.91)	3.96 (1.42-11.04) / 3.68 (1.32-10.21)
5th year	0.74 (0.18-3.01) / 0.80 (0.20-3.25)	0.00 (.-.) / 0.00 (0.00-.)	0.73 (0.23-2.30) / 0.81 (0.26-2.54)
6-10th year	0.47 (0.07-3.37) / 0.48 (0.07-3.44)	0.00 (0.00-.) / 0.00 (0.00-.)	0.36 (0.05-2.57) / 0.36 (0.05-2.61)
ANXIETY / OCD			
Overall	1.69 (1.31-2.17) / 1.87 (1.46-2.41)	1.90 (1.36-2.66) / 2.10 (1.50-2.93)	1.81 (1.43-2.28) / 2.00 (1.58-2.51)
1st year	1.73 (0.80-3.72) / 2.06 (0.97-4.40)	2.55 (0.92-7.02) / 2.81 (1.02-7.71)	1.92 (1.01-3.65) / 2.26 (1.20-4.27)
5th year	1.83 (1.23-2.71) / 2.02 (1.37-3.00)	2.12 (1.24-3.64) / 2.37 (1.39-4.06)	1.89 (1.31-2.71) / 2.10 (1.46-3.01)
6-10th year	1.99 (1.29-3.06) / 2.21 (1.44-3.39)	1.95 (1.09-3.49) / 2.18 (1.22-3.89)	1.99 (1.32-3.01) / 2.20 (1.46-3.32)
FATIGUE			
Overall	1.80 (1.50-2.17) / 1.75 (1.45-2.10)	1.81 (1.41-2.32) / 1.70 (1.33-2.18)	1.86 (1.56-2.22) / 1.82 (1.53-2.17)
1st year	3.83 (2.53-5.80) / 4.15 (2.75-6.25)	4.96 (2.90-8.49) / 5.04 (2.96-8.58)	4.31 (2.97-6.27) / 4.60 (3.18-6.66)
5th year	1.84 (1.37-2.48) / 1.82 (1.35-2.45)	1.76 (1.16-2.67) / 1.77 (1.17-2.68)	1.81 (1.36-2.42) / 1.82 (1.36-2.43)
6-10th year	1.81 (1.28-2.55) / 1.71 (1.22-2.41)	1.69 (1.06-2.70) / 1.54 (0.96-2.46)	1.85 (1.33-2.57) / 1.76 (1.27-2.44)

Supplementary table S5. Sensitivity analysis with Cox cause-specific risk estimates from the main model (right column) compared to risk estimates when excluding individuals with no prior history of any mental health events including fatigue (left column) and individuals with no prior psychotropic drug use <24 months prior to diagnosis of ITP (center column)

Abbreviations: ITP = immune thrombocytopenia, OCD = obsessive compulsive disorder, CI = confidence intervals

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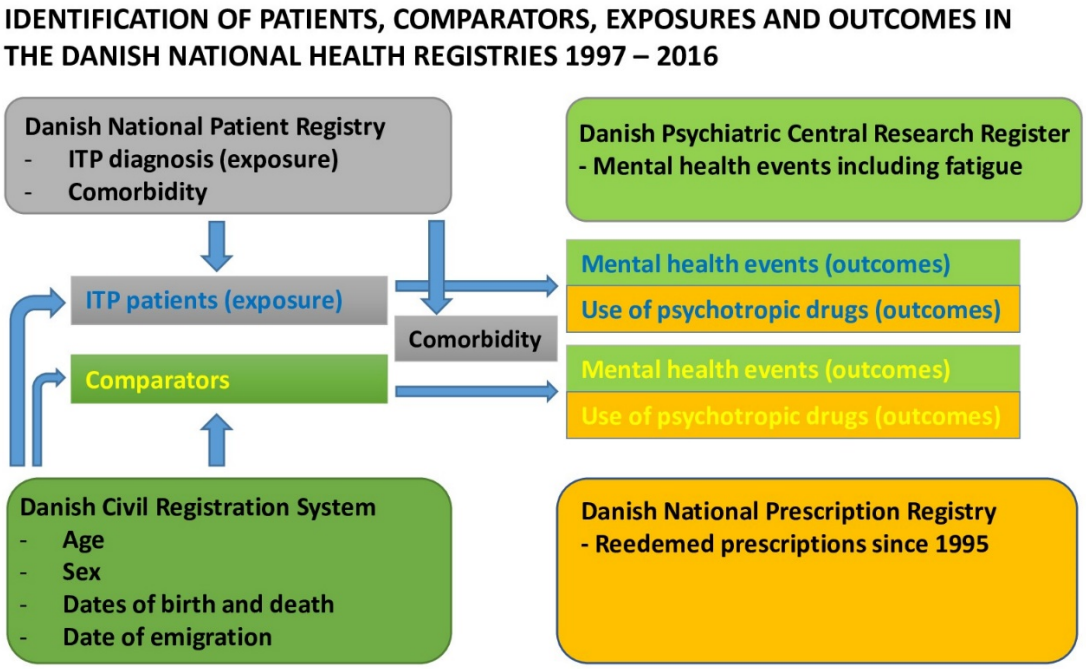
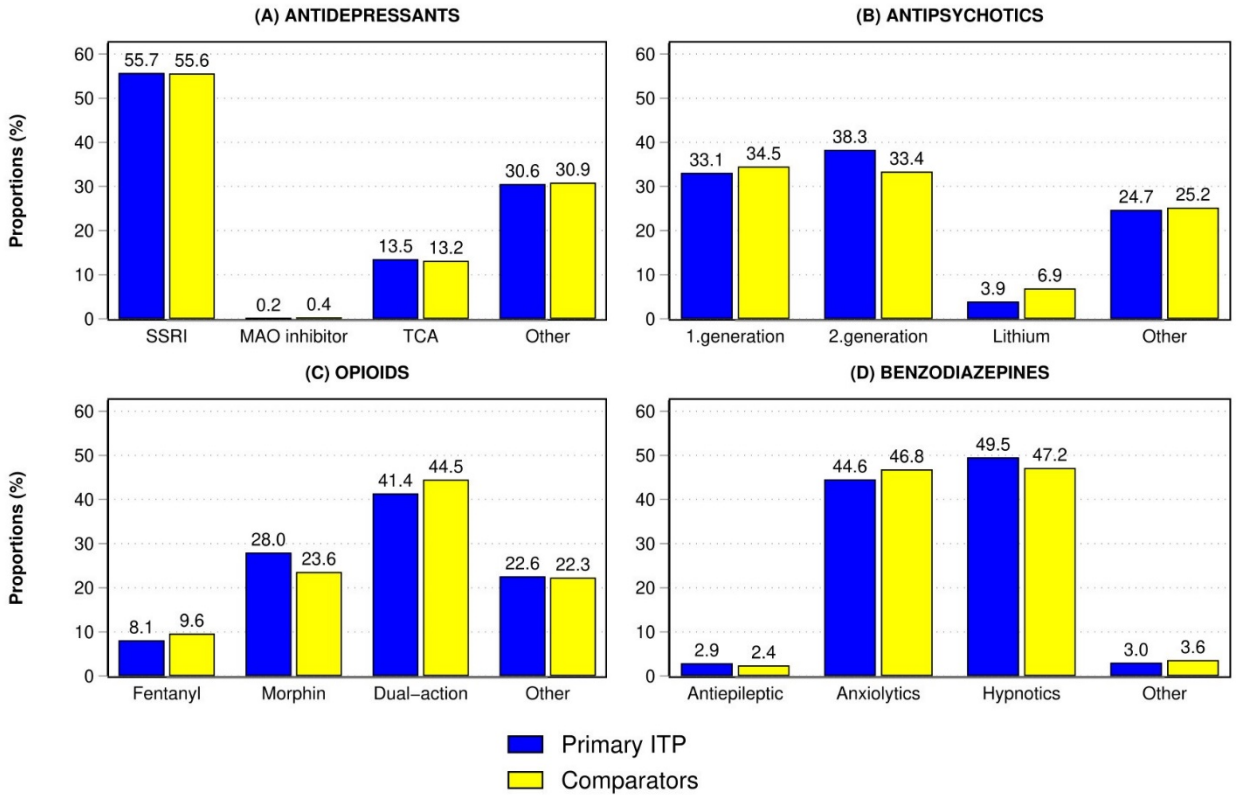
SUPPLEMENTARY FIGURE TITLES & LEGENDS

Supplementary figure S1. Model illustrating the applied registries and their data



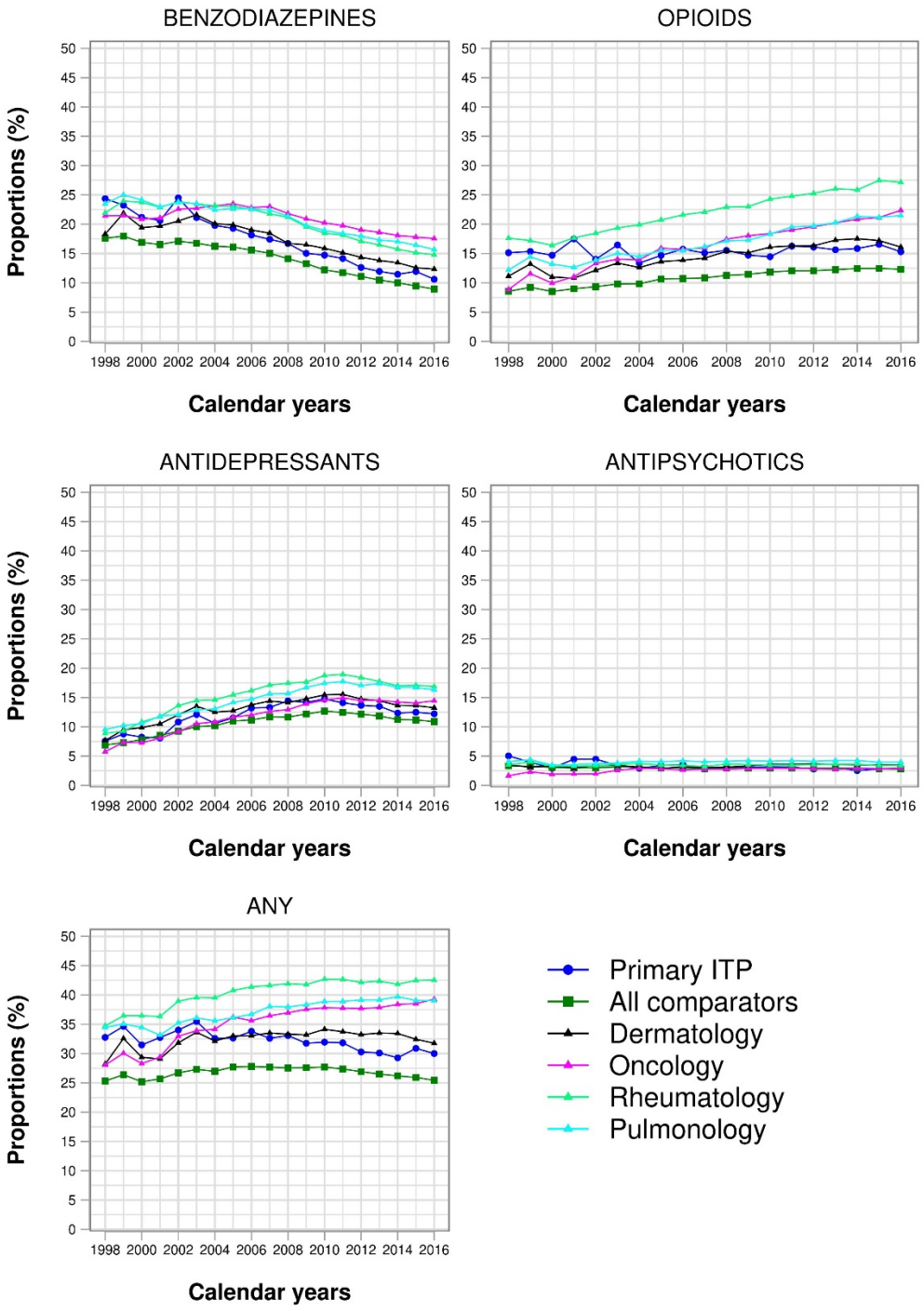
Supplementary figure S1. Illustration of the applied Danish health registries and which types of data were drawn from where. Patients (exposed) and comparators (non-exposed) were identified through the Danish National Patient Registry and Civil Registration System, while the Danish Psychiatric Central Research Register and National Prescription Registry were used to define and identify outcomes of interest (mental health events including fatigue, psychotropic drugs)

Supplementary figure S2. Subgroups of all psychotropic drugs distributed by patients with primary ITP and general population comparators



Supplementary figure S2. Illustration of the distributions of subgroups of drugs within each category of psychotropic drugs. Blue bars represent primary ITP and yellow comparators. No notable differences were found.

Supplementary figure S3. Prevalence proportions of psychotropic drugs in patients with primary ITP and general population comparators sorted by calendar-year, including comparators sampled on their hospital contacts within various specialties



Supplementary figure S3. Illustration of proportions of patients and comparators receiving a minimum of one prescription of a psychotropic drug in a year with full follow-up compared with the general population. We sampled comparator-individuals with a minimum of one known hospital contact within four medical specialties: dermatology, oncology, rheumatology, and pulmonology