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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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N. Mannering, D.L. Hansen and H. Frederiksen conceived the study idea. N. Mannering, D.L. Hansen, A. Pottegård, K. Andersen and H. Frederiksen designed the study. N. Mannering and H. Frederiksen applied for funding. N. Mannering and D.L. Hansen performed data analyses. N. Mannering wrote first draft. All authors read and approved the final version of the manuscript.

Data-sharing statement

All analyses were performed without access to detailed patient medical files. The authors are prohibited to share national health data or grant access to the data according to Danish law. Access to data can be made upon request through applications and contacts to the relevant Danish authorities.

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Abstract

Patients with primary immune thrombocytopenia (ITP) suffer from reduced survival and quality of life, but the underlying reasons for this are largely undescribed. Mental health and the use of psychotropic drugs in ITP is unknown.

We investigated the risk of hospital registered mental health events including fatigue and the use of psychotropic drugs in adult patients with ITP compared with the general population, using nationwide registry-data.

We identified 3,749 patients with ITP and 149,849 age-sex matched general population comparators in the Danish Health Registries in the period 1997-2016. The median age was 60 years (IQR 40-73) and 53% were women. We followed the individuals for incident mental health events and estimated the use of psychotropic drugs over calendar-years and in temporal relation to diagnosis of ITP.

The first year cumulative incidence of any mental health event was 2.3% (95% confidence interval, 1.9-2.9) in patients and 0.7% (0.6-0.7) in comparators, yielding an adjusted cause-specific hazard ratio (csHR) of 3.57 (2.84-4.50). The corresponding estimates for depression were 1.2% (0.9-1.6) and 0.3% (0.3-0.4) respectively, with an adjusted csHR of 3.53 (2.56-4.85). We found similar findings for anxiety and fatigue, but risks generally diminished after 1-5 years. The use of opioids, antidepressants, and benzodiazepines increased in temporal relation to diagnosis of ITP.

The risk of mental health events and the use of psychotropic drugs is higher in adult patients with ITP compared with the general population, and has a temporal relation to diagnosis of ITP emphasizing that mental health in ITP is a concern.

Introduction

Primary immune thrombocytopenia (ITP) is a disease characterized by accelerated autoimmune destruction of platelets and impaired bone marrow platelet-production, and requires a diagnostic process to exclude other causes of thrombocytopenia.[1-3] Both the incidence and prevalence of ITP increases with age and has increased during the past decades, making ITP an increasing health burden in Western populations.[4,5]

Both survival and quality of life is reduced in patients with ITP compared to the general population, but apart from bleeding tendency, the underlying mechanisms behind most health events in ITP are not well understood.[6-10] Studies suggest that this effect is mediated both by ITP disease in itself and associated factors, as well as immediate and late effects from treatments, e.g. the psychiatric side effects of high-dose corticosteroids.[11-15] Patients with ITP suffer from complications such as pronounced fatigue and social isolation, with the latter known to be associated with depression and lower quality of life.[16,17] The risk of major bleeding in ITP is low, but the fear of bleeding is present in many patients with ITP and associated with large declines in quality of life.[18,19] Despite major gains in the number of available treatments for ITP over the past decades, the health related quality of life in ITP is generally reduced and comparable to that of cancer patients.[7] This results in impaired physical and mental health, and affects social relations and work life.[7,10] The cross-sectional I-WISH worldwide study reported of high prevalence of fatigue in ITP and low levels of emotional well-being, arising from both low energy levels and fear of the ITP disease aggravating.[20,21] Fatigue is also known as a common symptom in ITP occurring in up to 39% of adult patients, and correlated with the severity of the ITP disease in terms of low platelet counts as well as the levels of inflammation.[22,23] The mechanisms underlying fatigue specifically in ITP and autoimmune disease in general are not well-understood, but likely involve multiple physiological processes.[24] The socioeconomic impact of ITP in terms of reduced working hours, work productivity, and increased risk of future unemployment could also worsen mental health in ITP.[20,25]

Taken together it is unknown how these factors may affect mental health, or if the use of psychotropic drugs is increased in adults with ITP. Providing clinicians with such knowledge and identifying potential mental health risk factors could improve management and quality of life in patients with ITP.

We assessed the risk of mental health events and the mental health burden by studying hospital registered mental health events including fatigue, and the use of psychotropic drugs in adult patients with ITP compared with the general population, using a large nationwide population-based cohort study with full follow-up.

Methods

Data sources

We used the public Danish health registries to identify patients, comparators, covariates and outcomes. Details on the application of each registry and an overview of data extraction can be found in the supplementary material (supplementary figure S1). In general, the methods applied are described in details in previous studies by us.[8,26]

Identification of patients, comparators, mental health events and drug use

We identified patients with ITP in the Danish National Patient Registry (DNPR) during 1997-2016, and assigned each patient with up to 40 age-sex matched comparators without ITP from the general population through the Danish Civil Registration System (DCRS). Matched individuals had the same sex and year of birth as their respective index patient. Patients with secondary ITP, Evans syndrome, and thrombocytopathies were excluded. All individuals were followed for the incident mental health events: schizophrenia/psychosis, depression, mania and bipolarity, anxiety/obsessive-compulsive disorder (OCD), fatigue, and a first-ever category with the first registration of any of the five aforementioned (supplementary table S1). We acknowledge that fatigue is not a psychiatric disorder per se, but patients often complain of fatigue, that may be a significant mental health burden. Therefore, we opted to include fatigue in the category "any mental health event". We also estimated the use of the psychotropic drugs: antidepressants, antipsychotics, benzodiazepines, opioids, and a first-ever category (supplementary table S1). The prevalence of both mental health events and psychotropic drug use prior to ITP diagnosis was also estimated.

We identified mental health events including fatigue in the DNPR, and psychotropic drug use was estimated through reimbursed prescriptions in the Danish National Prescription Registry (NPR), using this as a proxy measure of mental health burden.

The prevalent comorbidity was based on diagnoses registered in the DNPR before or on index date.

Statistical analyses

Baseline characteristics were presented as medians with interquartile range (IQR) for age, and percentages with 95% confidence intervals (95% CI) for distributions of sex, age-groups, prevalent comorbidities, prevalent mental health events, and prevalent use of psychotropic drugs. Comorbidity-score was calculated as means with 95% CIs of all prevalent comorbidity-covariates.

We used Cox proportional hazard and Fine-Gray regression to estimate unadjusted and adjusted cause-specific hazard ratios (csHR) and subdistribution hazard ratios for mental health events including fatigue in patients with ITP compared with the general population. We adjusted analyses for the effects of calendar decade of diagnosis, the defined comorbidities as dichotomous variables, and the residual confounding of age and sex.[27] The absolute risk of mental health events was estimated as cumulative incidences. Death and emigration served as competing events.

For psychotropic drug use, we estimated the monthly incidence-rates (IR) per 100-personyears (PY), incidence-rate-ratios (IRR), and incidence-rate-differences (IRD). We also estimated the prevalence proportions of patients and comparators receiving a minimum of one prescription in a given year within each category of psychotropic drugs. This was done for both calendar-years and for each year in a period 5 years prior to and 10 years after diagnosis of ITP.

All analyses were done separately for each outcome for set of patients with ITP and their respective general population comparators.

Please refer to supplementary material for details regarding methodical approaches and considerations.

Ethics approval

Registry-based research does not require Ethic Committee approval according to Danish law.

Results

We included 3,749 patients with ITP and 149,849 age-sex matched general population comparators, yielding a total of 153,598 individuals (Table 1). The total follow-up time was 21,753 PY (median 4.9 years) for ITP and 1,031,241 PY (median 6.2 years) for comparators.

Women comprised 53% and median age was 60 years (IQR 40-73) in both patients and comparators. The age-groups (18-59 years, 60+ years) were equally distributed between patients and comparators, and 39% were diagnosed with ITP in the period 1997-2006 and 61% in 2007-2016.

The mean comorbidity-score was 0.52 (95% CI 0.50-0.55) for ITP and 0.29 (0.28-0.29) for comparators. Among patients, 3.5% (2.9-4.1) had a comorbidity-score >2 while this only applied for 1.3% (1.2-1.3) of the comparators (Table 1).

At the time of ITP diagnosis, depression was prevalent among 3.9% (3.3-4.6) of patients vs. 2.8% (2.7-2.9) in comparators. 2.0% (1.6-2.5) of patients and 0.8% (0.8-0.9) of comparators had prevalent fatigue. Any mental health event was prevalent in 7.2% (6.4-8.1) of patients and 5.1% (5.0-5.2) of comparators (Table 1).

With the exception of antipsychotics, the prevalent use of psychotropic drugs up to 24 months prior to diagnosis of ITP was higher for all drug-groups in patients compared with comparators, with the highest use found in benzodiazepines (21% in patients and 16% in comparators) (Table 1).

Cumulative incidences and risk of mental health events

Mental health events and fatigue were more frequently registered in patients with ITP compared with the general population after index date, but differences generally diminished or equalized over time. The first year cumulative incidence of any mental health event was 2.3% (1.9-2.9) in patients and 0.7% (0.6-0.7) in comparators (Figure 1, supplementary table S3), with the highest subgroup incidence found in depression (1.2% (0.9-1.6) in patients and 0.3% (0.3-0.4) in comparators). The remaining subgroups also differed significantly during first year. Most cumulative incidence differences diminished (Figure 1, supplementary table S3), but persisted throughout the 5th year for depression and the 10th year for anxiety/OCD and fatigue.

The first year cumulative incidence of any mental health event in males with ITP was 2.1% (1.5-2.8) and 2.6% (1.9-3.4) in females (supplementary table S3). The corresponding numbers for comparators were 0.6% (0.5-0.6) and 0.7% (0.7-0.8), respectively. Similar differences during first year were found across age groups (18-59 and 60+ years) and calendar-years (supplementary table S3).

For all stratified groups, significant differences between patients and comparators persisted up to 10 years after diagnosis of ITP, with the largest differences found in the period 2007-2016 (supplementary table S3).

The overall risk of any mental health event was elevated with an adjusted csHR of 1.56 (1.38-1.76), and most pronounced during the first year where csHR was 3.57 (2.84-4.50) (Figure 2, supplementary table S4). The largest overall risk was found in fatigue with an adjusted csHR of 1.86 (1.56-2.22), and significantly elevated overall estimates were also found for depression and anxiety/OCD.

The risk during the first year was elevated for all subgroups. Fatigue was most pronounced with a first year adjusted csHR of 4.31 (2.97-6.97) followed by depression with a csHR of 3.53 (2.56-4.85). Risks declined to that of the general population for depression over time, but remained elevated for both anxiety/OCD and fatigue even after 10 years (Figure 2, supplementary table S4).

The overall risk of any mental health event in ITP did not differ across sex or age-groups (Figure 2, supplementary table S4). Calendar-year stratified analyses showed a significant increase in csHR from 1.28 (1.08-1.53) in 1997-2006 to 1.93 (1.63-2.27) in 2007-2016 (p-value <0.001 when applying the Altman-Bland test of interaction) (Figure 2, supplementary table S4).

Adjusted subdistribution hazard ratios taking competing events (death and emigration) into account generally lowered estimates towards the null-association, but remained significantly elevated for most subgroups and calendar-time periods (supplementary table S4).

Use of psychotropic drugs

Psychotropic drugs usage was elevated for patients with ITP compared with the general population, both in temporal relation to diagnosis of ITP, and over calendar-years.

The use of benzodiazepines was significantly elevated in patients in the year preceding diagnosis of ITP, and remained elevated in the first year after diagnosis (Figure 3). The 6-month IRRs between the incidences of new benzodiazepine prescriptions in patients and comparators were significantly elevated the entire period 24 months before and after diagnosis of ITP, with the largest difference in 0-6 months after diagnosis with an IRR of 1.85 (1.69-2.02) (table 2). The IRD peaked 0-6 months after ITP with 15.3 (12.5-18.2) more prescriptions/100-PY in patients vs. comparators, while the general use of benzodiazepines for both patients and comparators declined continuously over calendar-years by approximately 50% (Figure 3).

For antidepressants, the IRR was slightly elevated in the period 6 months before to 18months after diagnosis of ITP, with a peak of 1.24 (1.03-1.45) during 12-18months after ITP. The IRD was 1.67 (0.34-2.99) in favor of the patients in the 6 months preceding ITP diagnosis, and remained elevated throughout 18 months after diagnosis. The overall use of antidepressants increased slightly over calendar-years, but diminished after 2010 (Figure 3).

For opioids, the IRR between patients and comparators was significantly elevated in the 18 months preceding diagnosis of ITP, and peaking at 2.19 (1.95-2.44) in the 0-6month interval after diagnosis (table 2). The IRD also peaked in this interval with 11.11 (8.89-13.33) more prescriptions/100-PY among patients vs. comparators, and remained elevated >5.0 throughout all 24 months after ITP.

We did not find any differences between patients and comparators with regards to distribution of subgroups of drugs based on their ATC-codes and modes of action (supplementary figure S2).

Sensitivity analyses

The two sensitivity analyses (supplementary materials) excluding either all individuals with any history of any mental health event including fatigue or all individuals with any prior use of psychotropic drugs up to 24 months before index date, did not change results significantly (supplementary table S5). We also repeated the estimates of the category any mental health event with prior exclusion of fatigue in the

definition of any mental health event. This lowered the adjusted csHR from 1.56 (1.38-1.76) to 1.47 (1.27-1.70) (supplementary table S4).

We found that comparators sampled by affiliation to departments of pulmonology and rheumatology were more likely to have a higher use of psychotropic drugs than patients with ITP (supplementary figure S3).

Discussion

Using Danish nationwide health registries, we found an elevated risk of mental health events including fatigue among patients with ITP compared with the general population. The risks were most pronounced in the early years after diagnosis of ITP, however persisted for anxiety/OCD and fatigue. Patients with ITP also have an increased use of benzodiazepines, antidepressants and opioids, in temporal relation to diagnosis of ITP, mainly in the year preceding ITP diagnosis and in the following early years.

Comorbidity

Prevalent comorbidity was significantly more frequent among patients compared with the general population, but we adjusted all analyses for potential confounding and effect modifications. Previous studies have found that both prevalent and incident comorbidity is more frequent in patients with ITP than among the general population.[8] Comorbidity can impact both quality of life and mental health negatively, which could partly explain the increased prevalence of mental health events including fatigue, and prevalent use of psychotropic drugs in patients with ITP.[28,29]

Risks

We found an overall increased risk of hospital diagnosed depression, anxiety/OCD and fatigue in patients with ITP, with the risk of the latter two persisting over the entire study period. Furthermore, the risks for all subgroups of mental health events including fatigue were significantly elevated in the first year after diagnosis of ITP. Possible explanations for this variation over time could be an increased clinical focus and intervention on mental health events following the diagnosis of ITP, or that the mental impact of both diagnosis and treatment materializes in the immediate aftermath. However, the persisting risk of anxiety/OCD and particularly fatigue indicates that this patient group suffers from long-term mental health burdens. ITP is often a chronic autoimmune disease with multiple relapses and remissions. This applies especially to the elderly and comorbid population, where both the ITP disease in itself, the treatment, and the preexisting comorbidity burden could explain the reduced mental health and quality of life as seen in other chronic diseases.[30,31] Persistent fatigue has been described previously in ITP.[17,24,32] However, our

outcome was based on a hospital registered fatigue diagnosis possibly capturing a more severe entity. This could underestimate the true incidence of fatigue since many patients with ITP are not necessarily routinely screened for and registered with fatigue. Fatigue pathogenesis is unknown, but likely multifactorial.[32] A recent study argues that the immune suppression contributes to fatigue and does not alter the mechanisms underlying ITP, thereby not improving long-term outcomes such as quality of life and fatigue.[1] Platelets are involved in a plethora of immune reactions, and contain large amounts of circulating serotonin in their granules that they release in relation to both hemostasis and immune reactions.[33-35] Low levels of serotonin are related to both depression and fatigue.[36] This could indicate that low platelet counts are linked to low serotonin levels, causing both mental and immunological problems.[12] Whether patients with ITP and fatigue could benefit from therapy targeted at increasing levels of serotonin requires additional clinical studies, and the thrombotic risk associated with high serotonin levels should in that case also be considered.[37] Fatigue was included in the definition of the category any mental health event, but our analysis excluding fatigue from this category did not change results.

The subdistribution hazard ratios for mental health events including fatigue were generally lower than the csHR estimates, but remained significant. This indicates the presence of death as competing risk albeit minor. The survival is reduced both in patients with ITP, and in severe psychiatric disorders requiring hospitalization.[6,8,38,39]

The risk of any hospital registered mental health event including fatigue was higher in 2007-2016 compared with 1997-2006. The incidence of psychiatric disorders in Denmark has increased over the past decades, mainly due to earlier detection and awareness of psychiatric disorders.[40] Patients with ITP and preexisting comorbidities in a clinical course could be more prone to referral to psychiatric assessment than comparators, and this could inflate our estimates of diagnoses, but is unlikely to affect the psychotropic drug usage.

Psychotropic drugs

The reasons for the increased use of benzodiazepines in the year preceding ITP are unclear. It could be early ITP symptoms (e.g. fatigue) related to the underlying immunological processes, misinterpreted as anxiety or depression by the patients' general practitioner. The increase in the years after diagnosis of ITP could be explained by the immediate mental health burden following diagnosis, or treating side-effects from ITP-treatment e.g. insomnia from corticosteroids.[41] The use and indications of benzodiazepines are generally broad, and associated with multiple side-effects.[41,42] Long-term use is generally not recommended particularly in the elderly population in Denmark, and our data indicate that the use among

patients with ITP declines to the levels of the general population.[42] We found that risk of anxiety/OCD was highest in the first years following diagnosis of ITP, which could explain why pharmacological treatment is only necessary in a limited period. The use of benzodiazepines generally declined over calendar-years for both patients with ITP and comparators, probably attributable to increased regulation.[43]

The increased use of opioids prior to and after diagnosis of ITP could be due to the detection of conditions requiring analgesics during clinical follow-up for ITP, or pain associated with ITP itself, e.g. post-operative pain after splenectomy or status bone-marrow biopsies. Though decreasing in the recent years in Denmark, the use of opioids has generally increased over the past decades likely due to an ageing and more comorbid population, accompanied by increasing prevalence of chronic pain and disease.[44,45]

The use of antidepressants in Denmark is generally high, and though declining since 2011, prescribed to approximately 9% of the Danish adult population, with SSRIs being the most common drug.[46] This is in line with our findings of a declining trend over calendar-years in both ITP and comparators since 2010. However, there could be multiple reasons for the increased use in the early years after diagnosis of ITP. Patients with ITP are more burdened with comorbidity, which in turn is associated with an increased the use of antidepressants.[46] Some comorbidities could also become overt in the aftermath of ITP. A depression arising in the immediate aftermath of an ITP diagnosis as response to the chronic health burden constituted by the ITP disease in itself, as well as treatment, and the social consequences (e.g. reduced sports activity and fear of bleeding[19]), is also likely. Remission or acceptance of the ITP disease over time could explain both the declines in incident risk of depression, and the use of antidepressants relative to comparators.

A similar study also found elevated prescription rates for psychotropic drugs and incident risk of depression and anxiety in the years following a diagnosis of lymphoma, but similar to our findings both declined over time.[47] Finally, autoimmune disease and the underlying inflammation in general is associated with depression.[48]

Comparators affiliated with other medical specialties had a generally higher use of some psychotropic drugs, e.g. the benzodiazepine use was higher in comparators affiliated with pulmonology than in ITP. The reasons for this could be that high comorbidity equals a higher mental health burden, or that being followed at a hospital in itself makes them more likely to receive a prescription. Whether this also could be the explanation for the higher use among patients with ITP remains unclear, but besides an increased number of prescriptions in general, the proportion of hospital opioid prescribers is also increasing.[45]

Limitations

Despite being a nationwide study based on valid registry-data with full follow-up over 20 years, our study has limitations. We excluded secondary ITP, but some of these patients could potentially misclassify as ITP due to insufficient diagnostics of potential underlying disorders. However, we would expect this impact to be minor since secondary ITP constitutes a small proportion of patients with ITP.[8]

We lacked granular data on ITP treatment as well as biochemical data, e.g. accumulated corticosteroid-exposure and platelet counts, and it is difficult to assess causality from our findings in general. Our study spanned a 20-year period where demographics clinical practice, perception and treatment of both ITP and comorbidities has changed. The impact of this on our results is unknown.

We only included the first event of interest in our time-to-event analyses. This approach does not track any potential future improvements after the first registration of an e.g. depression. We included all psychotropic drug prescriptions over time for each individual to partly compensate for this. A higher need for antidepressants and benzodiazepines in patients compared with the general population persisted for up to two years after ITP diagnosis. However, our prescription data has limitations too, and the NPR does not allow for assessing indications for the prescribed drugs except for more recent time periods, treatment duration, or dosage from the prescribing physician.[49,50] Furthermore, we were not able to clarify whether individuals indeed used the entire package of a given redeemed psychotropic drug.

Conclusion

We have shown that the risk of mental health events including fatigue and the use of psychotropic drugs is elevated in patients with ITP compared with the general population, and has a temporal relation to diagnosis of ITP. Reasons for this are likely both related to the ITP disease and the management, but also due to other factors such as comorbidity or complications associated with ITP. Clinicians treating patients with ITP should be aware of such mental health problems during follow-up, and psychotropic drug use should be well indicated. Further clinical studies are required to identify risk groups that could benefit from potential interventions.

References

1. Provan D, Semple JW. Recent advances in the mechanisms and treatment of immune thrombocytopenia. EBioMedicine. 2022;76:103820.
2. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood. 2009;113(26):6511-6521.
3. Cines DB, Liebman H, Stasi R. Pathobiology of secondary immune thrombocytopenia. Semin Hematol. 2009;46(1 Suppl 2):S2-14.
4. Lawrie DA, Mannering N, Hansen DL, Frederiksen H. Time trends in incidence and prevalence of immune thrombocytopenia: A nationwide cohort analysis. Br J Haematol. 2023;202(3):690-692.
5. Salive ME. Multimorbidity in older adults. Epidemiol Rev. 2013;35:75-83.
6. Norgaard M, Jensen AO, Engebjerg MC, et al. Long-term clinical outcomes of patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. Blood. 2011;117(13):3514-3520.
7. McMillan R, Bussel JB, George JN, Lalla D, Nichol JL. Self-reported health-related quality of life in adults with chronic immune thrombocytopenic purpura. Am J Hematol. 2008;83(2):150-154.
8. Mannering N, Hansen DL, Pottegard A, Frederiksen H. Survival in adult patients with chronic primary and secondary immune thrombocytopenia: A population-based study. Transfusion. 2023;63(2):415-426.
9. Sestol HG, Trangbaek SM, Bussel JB, Frederiksen H. Health-related quality of life in adult primary immune thrombocytopenia. Expert Rev Hematol. 2018;11(12):975-985.
10. Mathias SD, Gao SK, Miller KL, et al. Impact of chronic Immune Thrombocytopenic Purpura (ITP) on health-related quality of life: a conceptual model starting with the patient perspective. Health Qual Life Outcomes. 2008;6:13.
11. Frederiksen H, Maegbaek ML, Norgaard M. Twenty-year mortality of adult patients with primary immune thrombocytopenia: a Danish population-based cohort study. Br J Haematol. 2014;166(2):260-267.
12. Sandvad M, Pedersen EA, Frederiksen H, Mannering N. Risk of infection in adult patients with Primary Immune Thrombocytopenia (ITP): A systematic review. Expert Rev Hematol. 2021;14(10):961-974.
13. Grover S, Sahoo S, Rijal R, Mehra A. Don't forget me in amidst of COVID-19 pandemic: A case series and review of literature on steroid associated psychiatric manifestations. Brain Behav Immun Health. 2021;18:100345.
14. McGrath P, Holewa H. The emotional consequences of corticosteroid use in hematology: preliminary findings. J Psychosoc Oncol. 2010;28(4):335-350.
15. Frederiksen H, Ghanima W. Response of first line treatment with corticosteroids in a population-based cohort of adults with primary immune thrombocytopenia. Eur J Intern Med. 2017;37:e23-e25.
16. Ge L, Yap CW, Ong R, Heng BH. Social isolation, loneliness and their relationships with depressive symptoms: A population-based study. PLoS One. 2017;12(8):e0182145.
17. Mitchell E, Frith J, Newton J. Fatigue and cognitive impairment in immune thrombocytopenic purpura remain stable over time: short report from a longitudinal study. Br J Haematol. 2019;186(5):777-781.
18. Arnold DM. Bleeding complications in immune thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2015;2015:237-242.
19. Zhou Z, Yang L, Chen Z, et al. Health-related quality of life measured by the Short Form 36 in immune thrombocytopenic purpura: a cross-sectional survey in China. Eur J Haematol. 2007;78(6):518-523.

20. Cooper N, Kruse A, Kruse C, et al. Immune thrombocytopenia (ITP) World Impact Survey (I-WISh): Impact of ITP on health-related quality of life. Am J Hematol. 2021;96(2):199-207.
21. Cooper N, Kruse A, Kruse C, et al. Immune thrombocytopenia (ITP) World Impact Survey (iWISh): Patient and physician perceptions of diagnosis, signs and symptoms, and treatment. Am J Hematol. 2021;96(2):188-198.
22. Newton JL, Reese JA, Watson SI, et al. Fatigue in adult patients with primary immune thrombocytopenia. Eur J Haematol. 2011;86(5):420-429.
23. Mathias SD, Bussel JB, George JN, McMillan R, Okano GJ, Nichol JL. A disease-specific measure of health-related quality of life for use in adults with immune thrombocytopenic purpura: its development and validation. Health Qual Life Outcomes. 2007;5:11.
24. Zielinski MR, Systrom DM, Rose NR. Fatigue, Sleep, and Autoimmune and Related Disorders. Front Immunol. 2019;10:1827.
25. Murphy GC, Athanasou JA. The effect of unemployment on mental health. J Occup Organ Psych. 1999;72(1):83-99.
26. Mannering N, Hansen DL, Moulis G, Ghanima W, Pottegard A, Frederiksen H. Risk of fractures and use of bisphosphonates in adult patients with immune thrombocytopenia-A nationwide population-based study. Br J Haematol. 2024;204(4):1464-1475.
27. Moller S, Bliddal M, Rubin KH. Methodical considerations on adjusting for Charlson Comorbidity Index in epidemiological studies. Eur J Epidemiol. 2021;36(11):1123-1128.
28. Ho C, Feng L, Fam J, Mahendran R, Kua EH, Ng TP. Coexisting medical comorbidity and depression: multiplicative effects on health outcomes in older adults. Int Psychogeriatr. 2014;26(7):1221-1229.
29. Pati S, Pati S, Akker MVD, Schellevis FFG, Jena S, Burgers JS. Impact of comorbidity on health-related quality of life among type 2 diabetic patients in primary care. Prim Health Care Res Dev. 2020;21:e9.
30. Ducat L, Philipson LH, Anderson BJ. The mental health comorbidities of diabetes. JAMA. 2014;312(7):691-692.
31. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829-3866.
32. Hill QA, Newland AC. Fatigue in immune thrombocytopenia. Br J Haematol. 2015;170(2):141-149.
33. Weyrich AS, Zimmerman GA. Platelets: signaling cells in the immune continuum. Trends Immunol. 2004;25(9):489-495.
34. Semple JW, Italiano JE Jr, Freedman J. Platelets and the immune continuum. Nat Rev Immunol. 2011;11(4):264-274.
35. Duerschmied D, Suidan GL, Demers M, et al. Platelet serotonin promotes the recruitment of neutrophils to sites of acute inflammation in mice. Blood. 2013;121(6):1008-1015.
36. Beikmann BS, Tomlinson ID, Rosenthal SJ, Andrews AM. Serotonin Uptake Is Largely Mediated by Platelets versus Lymphocytes in Peripheral Blood Cells. Acs Chem Neurosci. 2013;4(1):161-170.
37. Lopez-Vilchez I, Diaz-Ricart M, White JG, Escolar G, Galan AM. Serotonin enhances platelet procoagulant properties and their activation induced during platelet tissue factor uptake. Cardiovasc Res. 2009;84(2):309-316.
38. Nordentoft M, Wahlbeck K, Hallgren J, et al. Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. PLoS One. 2013;8(1):e55176.
39. Melo APS, Dippenaar IN, Johnson SC, et al. All-cause and cause-specific mortality among people with severe mental illness in Brazil's public health system, 2000-15: a retrospective study. Lancet Psychiatry. 2022;9(10):771-781.
40. Plana-Ripoll O, Momen NC, McGrath JJ, et al. Temporal changes in sex- and age-specific incidence profiles of mental disorders-A nationwide study from 1970 to 2016. Acta Psychiatr Scand. 2022;145(6):604-614.

41. Edinoff AN, Nix CA, Hollier J, et al. Benzodiazepines: Uses, Dangers, and Clinical Considerations. Neurol Int. 2021;13(4):594-607.
42. Johnson B, Streltzer J. Risks associated with long-term benzodiazepine use. Am Fam Physician. 2013;88(4):224-226.
43. Rosenqvist TW, Wium-Andersen MK, Wium-Andersen IK, Jorgensen MB, Osler M. Long-Term Use of Benzodiazepines and Benzodiazepine-Related Drugs: A Register-Based Danish Cohort Study on Determinants and Risk of Dose Escalation. Am J Psychiatry. 2024;181(3):246-254.
44. Nissen SK, Pottegard A, Ryg J. Trends of Opioid Utilisation in Denmark: A Nationwide Study. Drugs Real World Outcomes. 2019;6(4):155-164.
45. Pottegard A, Sorensen AMS, Olesen M, Rasmussen L. Opioid prescriber responsibility: A Danish drug utilization study. Br J Clin Pharmacol. 2023;89(4):1425-1430.
46. Forns J, Pottegard A, Reinders T, et al. Antidepressant use in Denmark, Germany, Spain, and Sweden between 2009 and 2014: Incidence and comorbidities of antidepressant initiators. J Affect Disord. 2019;249:242-252.
47. Ovlisen AK, Jakobsen LH, Kragholm KH, et al. Mental health among patients with non-Hodgkin lymphoma: A Danish nationwide study of psychotropic drug use in 8750 patients and 43 750 matched comparators. Am J Hematol. 2022;97(6):749-761.
48. Pryce CR, Fontana A. Depression in Autoimmune Diseases. Curr Top Behav Neurosci. 2017;31:139-154.
49. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2017;46(3):798-798f.
50. Harbi H, Pottegard A. Validation of the "Indication for Use" (INDO) Variable in the Danish National Prescription Registry. Epidemiology. 2024;35(1):1-6.

TABLES

Table 1. Baseline characteristics of patients with primary ITP and general population age-sex matched comparators

NAME	Primary ITP (%) (95% CI) (n=3,749)	Comparators (%) (95% CI) (n=149,849)
Women	53 (52-55)	53 (53-53)
Age (years, median (IQR))	60 (40-73)	60 (40-73)
PERIOD OF DIAGNOSIS		
1997-2006	39 (37-40)	39 (39-39)
2007-2016	61 (60-63)	61 (61-61)
AGE GROUPS		
18-59years	50 (49-52)	50 (50-50)
60+ years	50 (48-51)	50 (50-50)
PREVALENT COMORBIDITY		
Comorbidity-score (mean)	0.52 (0.50-0.55)	0.29 (0.28-0.29)
Low (0)	64.4 (62.8-65.9)	78.2 (78.0-78.4)
Intermediate (1-2)	32.1 (30.6-33.6)	20.6 (20.4-20.8)
High (>2)	3.5 (2.9-4.1)	1.3 (1.2-1.3)
PREVALENT DRUG PRESCRIPTION <24 MONTHS BEFORE ITP		
Antidepressants	14.3 (13.2-15.4)	11.1 (11.0-11.3)
Antipsychotics	3.7 (3.2-4.4)	3.2 (3.2-3.3)
Opioids	20.3 (19.0-21.6)	13.8 (13.6-14.0)
Benzodiazepines	21.0 (19.7-22.4)	16.1 (15.9-16.3)
Any psychotropic drug	38.7 (37.2-40.3)	30.2 (30.0-30.5)
PREVALENT MENTAL HEALTH EVENTS INCLUDING FATIGUE		
Schizophrenia / Psychosis	1.2 (0.9-1.6)	0.9 (0.9-1.0)
Depression	3.9 (3.3-4.6)	2.8 (2.7-2.9)
Mania / Bipolarity	0.2 (0.1-0.4)	0.4 (0.4-0.4)
Anxiety / OCD	0.9 (0.7-1.3)	1.2 (1.1-1.2)
Fatigue	2.0 (1.6-2.5)	0.8 (0.8-0.9)
Any mental health event	7.2 (6.4-8.1)	5.1 (5.0-5.2)
Number of mental health events >1	1.0 (0.7-1.4)	0.9 (0.8-0.9)

Table 1. Baseline characteristics for primary ITP patients and age-sex matched general population comparators. 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, IQR = interquartile range, OCD = obsessive compulsive disorder, CI = confidence interval

Table 2. Incidence-rates (IR) per 100 person-years, incidence-rate-differences (IRD) and incidence-rate-ratios (IRR) for *new* psychotropic drug use in 6-month intervals in patients with primary ITP compared with the general population

	Primary ITP	**Comparators**		
Name	**Incidence-rate (95%CI)**	**Incidence-rate (95%CI)**	**IRR (95%CI)**	**IRD (95%CI)**
INCIDENCES YEAR -2 – -1.5				
Antidepressants	6.22 (5.16-7.51)	5.56 (5.39-5.74)	1.12 (0.92-1.35)	0.66 (-0.52-1.85)
Antipsychotics	1.52 (1.05-2.20)	1.72 (1.63-1.82)	0.88 (0.58-1.28)	-0.20 (-0.77-0.37)
Opioids	7.71 (6.52-9.12)	6.77 (6.58-6.97)	1.14 (0.95-1.35)	0.94 (-0.37-2.24)
Benzodiazepines	20.78 (18.72-23.06)	16.79 (16.48-17.09)	1.24 (1.11-1.38)	3.99 (1.81-6.17)
Any psychotropic drug	52.50 (49.04-56.21)	45.09 (44.57-45.61)	1.16 (1.09-1.25)	7.41 (3.79-11.03)
INCIDENCES YEAR -1.5 – -1				
Antidepressants	6.60 (5.50-7.93)	5.73 (5.55-5.91)	1.15 (0.95-1.39)	0.88 (-0.34-2.09)
Antipsychotics	1.74 (1.23-2.46)	1.71 (1.61-1.80)	1.02 (0.69-1.45)	0.03 (-0.58-0.65)
Opioids	8.98 (7.69-10.50)	7.17 (6.97-7.37)	1.25 (1.06-1.47)	1.81 (0.40-3.23)
Benzodiazepines	20.94 (18.87-23.23)	16.81 (16.51-17.12)	1.25 (1.12-1.38)	4.13 (1.93-6.32)
Any psychotropic drug	58.40 (54.70-62.34)	46.47 (45.94-47.00)	1.26 (1.17-1.34)	11.93 (8.08-15.78)
INCIDENCES YEAR -1 – -0.5				
Antidepressants	7.08 (5.93-8.44)	5.95 (5.78-6.14)	1.19 (0.99-1.42)	1.12 (-0.14-2.38)
Antipsychotics	1.68 (1.18-2.39)	1.71 (1.62-1.81)	0.98 (0.67-1.40)	-0.03 (-0.63-0.57)
Opioids	9.97 (8.60-11.56)	7.29 (7.09-7.49)	1.37 (1.17-1.59)	2.68 (1.19-4.17)
Benzodiazepines	20.46 (18.42-22.72)	16.83 (16.53-17.14)	1.22 (1.09-1.35)	3.63 (1.46-5.80)
Any psychotropic drug	59.78 (56.04-63.77)	48.04 (47.50-48.58)	1.24 (1.16-1.33)	11.75 (7.85-15.64)
INCIDENCES YEAR -0.5 – 0				
Antidepressants	7.75 (6.55-9.18)	6.09 (5.91-6.27)	1.27 (1.06-1.51)	1.67 (0.34-2.99)
Antipsychotics	1.58 (1.10-2.27)	1.73 (1.64-1.83)	0.91 (0.61-1.31)	-0.16 (-0.74-0.43)
Opioids	13.58 (11.95-15.44)	7.60 (7.40-7.80)	1.79 (1.56-2.04)	5.98 (4.23-7.73)
Benzodiazepines	22.91 (20.74-25.31)	16.65 (16.35-16.95)	1.38 (1.24-1.52)	6.26 (3.97-8.56)
Any psychotropic drug	70.97 (66.84-75.35)	48.84 (48.30-49.39)	1.45 (1.37-1.54)	22.12 (17.83-26.41)
INCIDENCES YEAR 0 – 0.5				
Antidepressants	8.34 (7.05-9.85)	6.90 (6.70-7.10)	1.21 (1.01-1.43)	1.44 (0.03-2.85)
Antipsychotics	2.54 (1.89-3.41)	1.89 (1.79-1.99)	1.34 (0.97-1.82)	0.65 (-0.11-1.41)
Opioids	20.47 (18.38-22.80)	9.37 (9.14-9.60)	2.19 (1.95-2.44)	11.11 (8.89-13.33)
Benzodiazepines	33.43 (30.67-36.43)	18.08 (17.77-18.41)	1.85 (1.69-2.02)	15.34 (12.45-18.24)
Any psychotropic drug	96.76 (91.68-102.13)	54.12 (53.54-54.70)	1.79 (1.69-1.89)	42.65 (37.39-47.90)
INCIDENCES YEAR 0.5 – 1				
Antidepressants	8.68 (7.32-10.30)	7.11 (6.91-7.32)	1.22 (1.02-1.45)	1.57 (0.08-3.07)
Antipsychotics	2.36 (1.72-3.25)	1.97 (1.87-2.08)	1.20 (0.84-1.65)	0.39 (-0.37-1.15)
Opioids	17.44 (15.44-19.69)	10.25 (10.01-10.50)	1.70 (1.50-1.92)	7.18 (5.06-9.31)
Benzodiazepines	24.45 (22.06-27.10)	18.94 (18.61-19.27)	1.29 (1.16-1.43)	5.51 (2.97-8.05)
Any psychotropic drug	82.64 (77.85-87.73)	56.95 (56.35-57.56)	1.45 (1.36-1.54)	25.69 (20.71-30.66)
INCIDENCES YEAR 1 – 1.5				
Antidepressants	9.06 (7.62-10.77)	7.32 (7.11-7.54)	1.24 (1.03-1.47)	1.73 (0.15-3.32)
Antipsychotics	1.86 (1.28-2.69)	2.01 (1.91-2.12)	0.92 (0.61-1.34)	-0.15 (-0.85-0.54)
Opioids	16.73 (14.73-19.02)	10.84 (10.58-11.10)	1.54 (1.35-1.76)	5.90 (3.74-8.05)
Benzodiazepines	23.49 (21.08-26.18)	19.12 (18.78-19.47)	1.23 (1.10-1.37)	4.38 (1.81-6.94)
Any psychotropic drug	78.47 (73.66-83.59)	58.35 (57.73-58.99)	1.34 (1.26-1.43)	20.12 (15.12-25.11)
INCIDENCES YEAR 1.5 – 2				
Antidepressants	8.34 (6.93-10.05)	7.44 (7.22-7.66)	1.12 (0.92-1.35)	0.90 (-0.66-2.47)
Antipsychotics	2.27 (1.61-3.21)	2.10 (1.99-2.22)	1.08 (0.74-1.53)	0.17 (-0.63-0.96)
Opioids	16.50 (14.45-18.84)	11.14 (10.87-11.41)	1.48 (1.29-1.70)	5.37 (3.16-7.57)
Benzodiazepines	24.68 (22.13-27.52)	19.51 (19.16-19.87)	1.26 (1.13-1.41)	5.17 (2.45-7.88)
Any psychotropic drug	79.50 (74.52-84.81)	59.81 (59.16-60.47)	1.33 (1.24-1.42)	19.69 (14.51-24.87)

Table 2. Incidence rates (IR), incidence rate ratios (IRR), and incidence rate differences (IRD) in patients with primary ITP and comparators, as 6-month interval estimates two years before and after diagnosis of ITP.
Abbreviations: ITP = immune thrombocytopenia, CI = confidence intervals

FIGURES

Figure Titles & Figure Legends

Figure 1. Cumulative incidence proportions for mental health events including fatigue

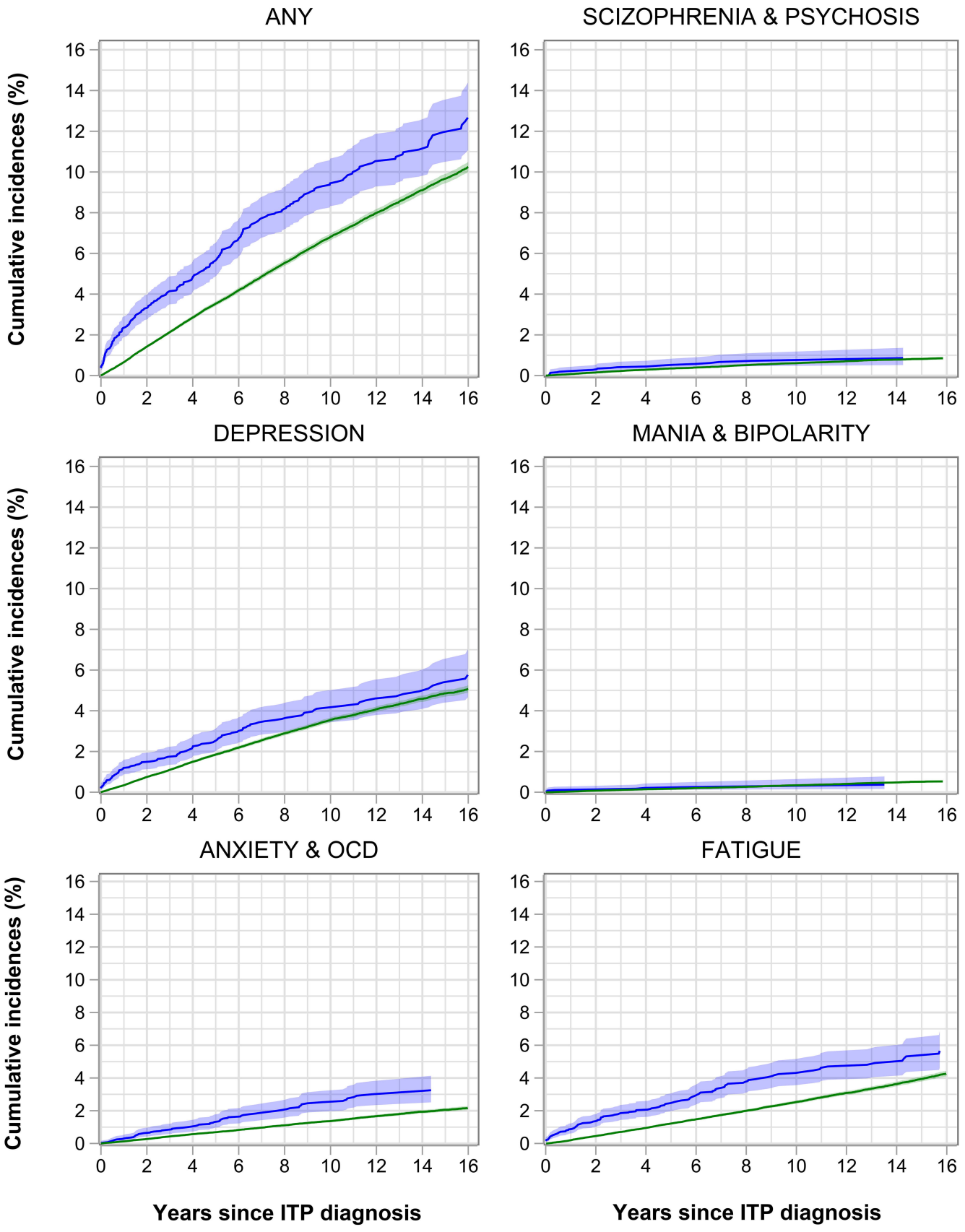
Figure 1. Cumulative incidences for different mental health events including fatigue. The category "Any" was the first-ever hospital registration of any of the other five groups. Cumulative incidences for patients with ITP were elevated for depression, anxiety or OCD, and fatigue compared with the general population.
Abbreviations: ITP = immune thrombocytopenia, OCD = obsessive-compulsive disorder

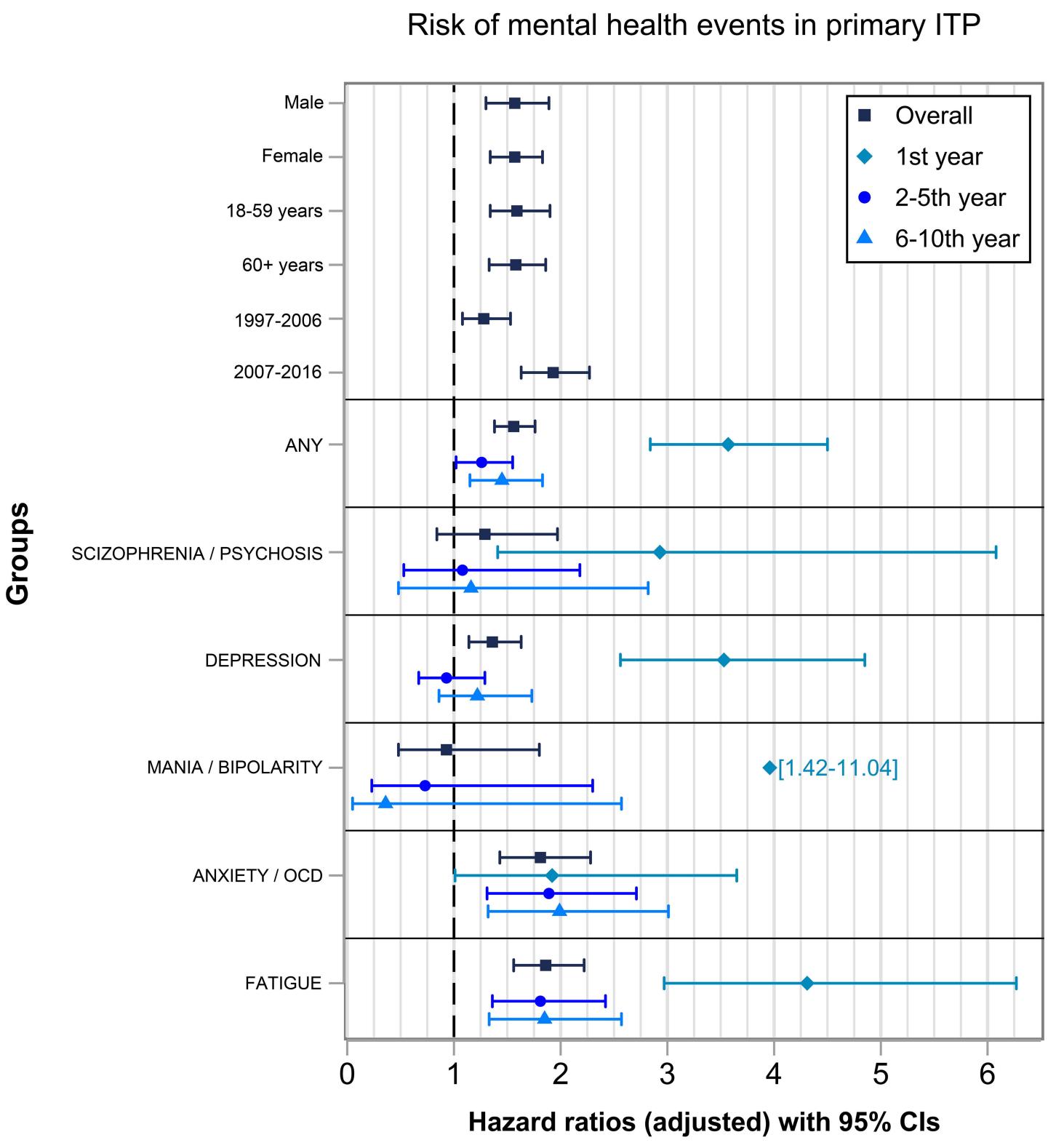
Figure 2. Hazard ratios for mental health events including fatigue in ITP compared with the general population

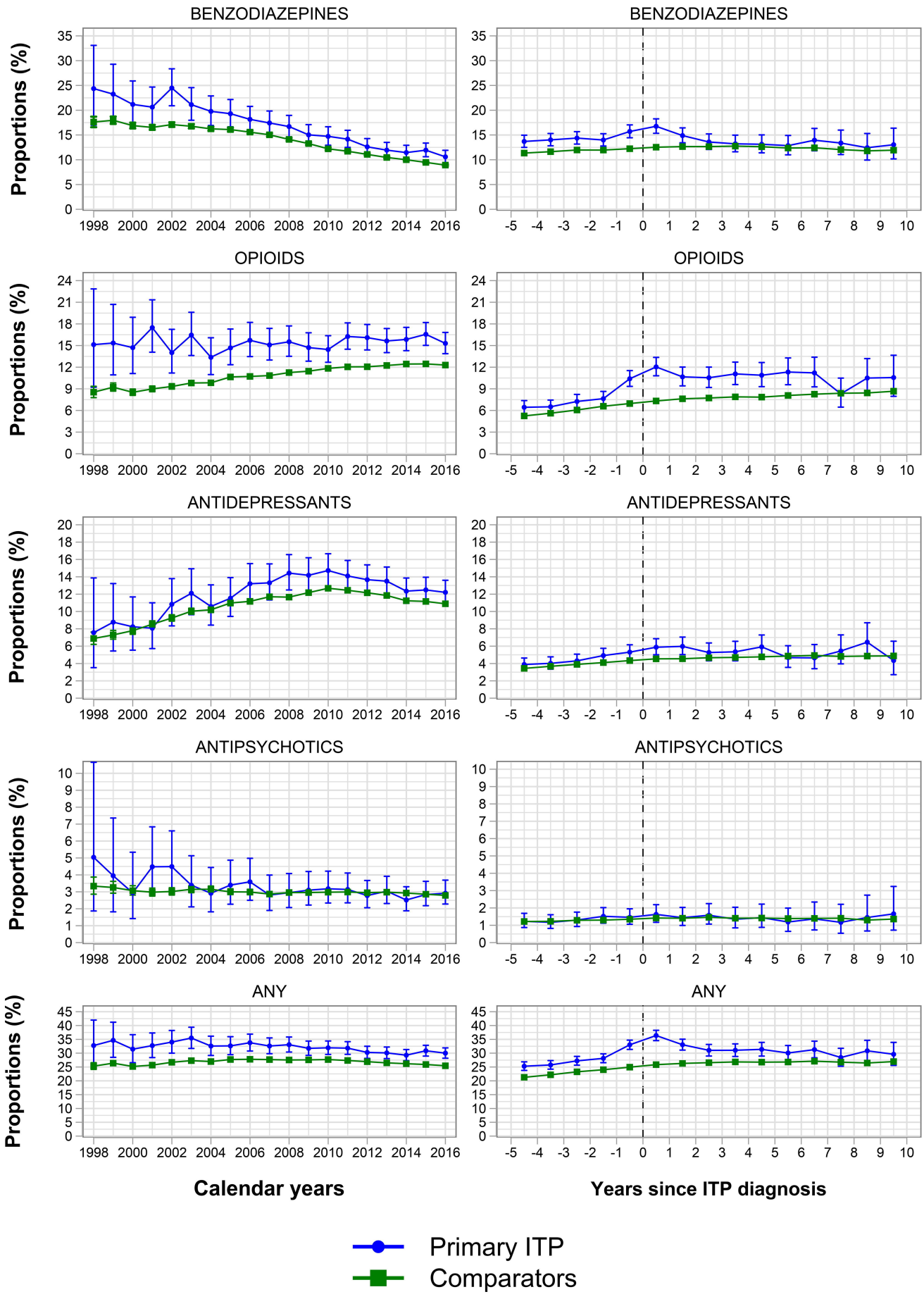
Figure 2. Graphic illustrations of hazard ratios for mental health events including fatigue, illustrating overall and time-splitted estimates as well as overall estimates stratified on age, sex and calendar-years. Risk was generally increased for most mental health events, with largest risk estimates in the first years. *Please note* that the confidence intervals for some 1st year risk estimates due to high right outliers are provided as text, in order to optimize the visual information in the graph.
Abbreviations: ITP = immune thrombocytopenia, OCD = obsessive compulsive disorder, CI = confidence interval

Figure 3. Prevalence proportions for psychotropic drugs in patients with primary ITP and general population comparators

Figure 3. Illustration of the use of psychotropic drugs measured as proportions of patients with ITP and comparators receiving a minimum of one registered prescription within a given year with full follow-up. Blue represents primary ITP, while green represents comparators.
Abbreviations: ITP = immune thrombocytopenia


ANY
SCIZOPHRENIA & PSYCHOSIS
DEPRESSION
MANIA & BIPOLARITY
ANXIETY & OCD
FATIGUE
Cumulative incidences (%)
Years since ITP diagnosis
Primary ITP
Comparators


Risk of mental health events in primary ITP
Male
Female
18-59 years
60+ years
1997-2006
2007-2016
ANY
SCIZOPHRENIA / PSYCHOSIS
DEPRESSION
MANIA / BIPOLARITY
ANXIETY / OCD
FATIGUE
Overall
1st year
2-5th year
6-10th year
[1.42-11.04]
Groups
0
1
2
3
4
5
6
Hazard ratios (adjusted) with 95% CIs


BENZODIAZEPINES
BENZODIAZEPINES
OPIOIDS
OPIOIDS
ANTIDEPRESSANTS
ANTIDEPRESSANTS
ANTIPSYCHOTICS
ANTIPSYCHOTICS
ANY
ANY
Proportions (%)
Calendar years
Years since ITP diagnosis
Primary ITP
Comparators

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)

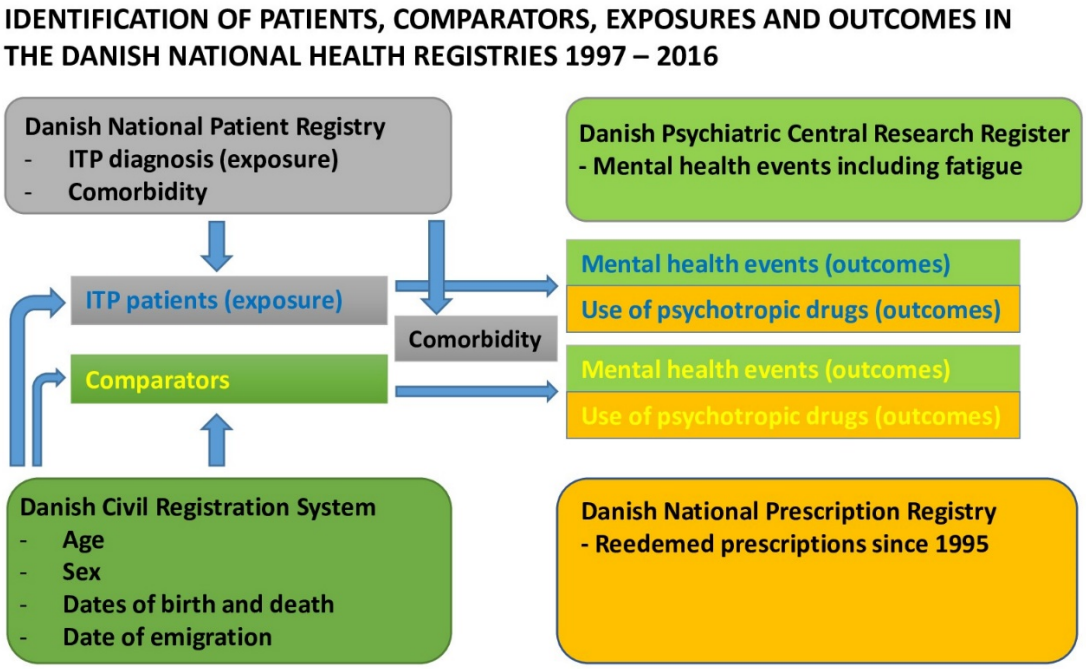
Abbreviations: ITP = immune thrombocytopenia, OCD = obsessive compulsive disorder, CI = confidence intervals

References

1. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2017;46(3):798-798f.
2. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-490.
3. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541-549.
4. Heden KE, Jensen AO, Farkas DK, Norgaard M. Validity of a procedure to identify patients with chronic idiopathic thrombocytopenic purpura in the Danish National Registry of Patients. Clin Epidemiol. 2009;1:7-10.
5. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011;39(7 Suppl):30-33.
6. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health. 2011;39(7 Suppl):54-57.
7. Pedersen CB. The Danish Civil Registration System. Scand J Public Health. 2011;39(7 Suppl):22-25.
8. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011;39(7 Suppl):38-41.
9. Mannering N, Hansen DL, Moulis G, Ghanima W, Pottegard A, Frederiksen H. Risk of fractures and use of bisphosphonates in adult patients with immune thrombocytopenia-A nationwide population -based study. Br J Haematol. 2024.
10. Mannering N, Hansen DL, Pottegard A, Frederiksen H. Survival in adult patients with chronic primary and secondary immune thrombocytopenia: A population-based study. Transfusion. 2023.
11. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676-682.
12. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011;11:83.
13. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496-509.
14. Latouche A, Allignol A, Beyersmann J, Labopin M, Fine JP. A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. J Clin Epidemiol. 2013;66(6):648-653.
15. Coviello V, Boggess M. Cumulative incidence estimation in the presence of competing risks. Stata J. 2004;4(2):103-112.
16. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ. 2003;326(7382):219.
17. Pottegard A, Friis S, Verdoodt F, Dehlendorff C, Hallas J, Kjaer SK. Use of prescription drugs among women diagnosed with epithelial ovarian cancer in Denmark. Acta Obstet Gynecol Scand. 2018.
18. Moller S, Bliddal M, Rubin KH. Methodical considerations on adjusting for Charlson Comorbidity Index in epidemiological studies. Eur J Epidemiol. 2021.

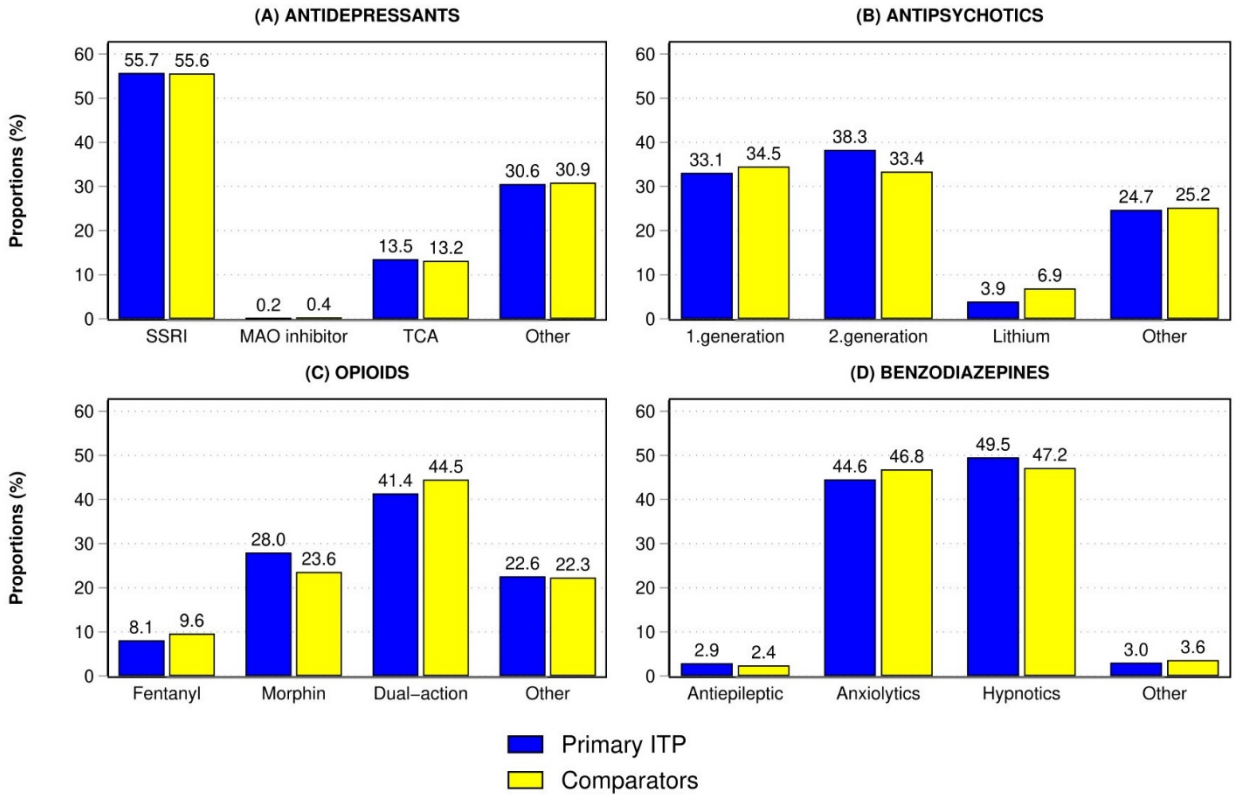
SUPPLEMENTARY FIGURE TITLES & LEGENDS

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



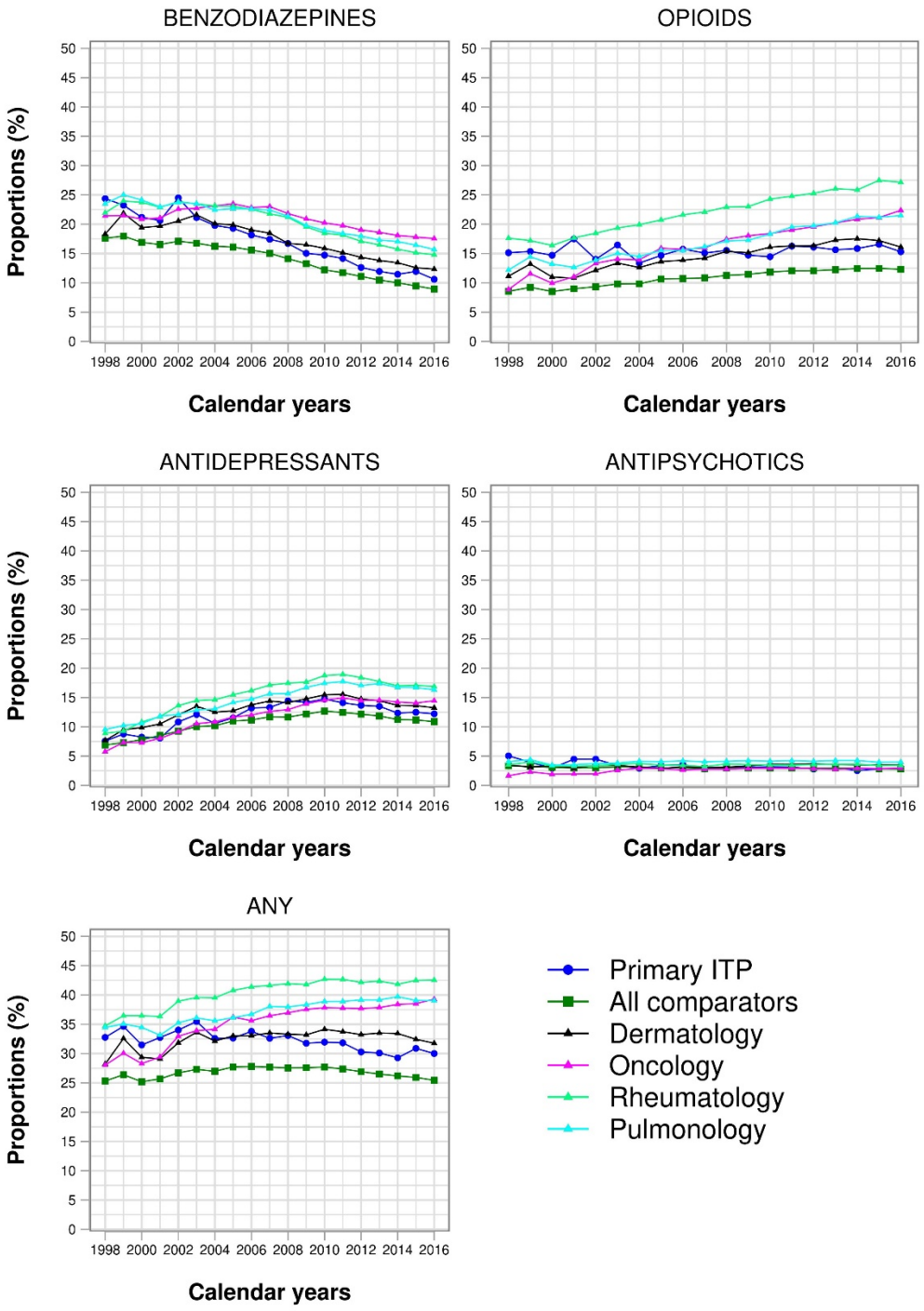
Supplementary figure S1. Illustration of the applied Danish health registries and which types of data were drawn from where. Patients (exposed) and comparators (non-exposed) were identified through the Danish National Patient Registry and Civil Registration System, while the Danish Psychiatric Central 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