

Psychiatric morbidity in people with autoimmune arthritides as a model of inflammatory mechanisms in mental disorders

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45 Abstract

46 Background

47 Rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA) are autoimmune illnesses,
48 characterized by chronic inflammation, and demonstrating differential associations with
49 psychiatric conditions.

51 Objective

52 In this matched-cohort study, we aimed to investigate whether the associations between these
53 inflammatory illnesses and mental disorders are predominantly the consequence of the burden
54 of the former, or whether common causes might underpin the susceptibility to both.

56 Methods

57 Using Czech national inpatient care data, we identified individuals with RA or axSpA during
58 1999-2012. We investigated the occurrence of psychiatric outcomes up-to 2017 using stratified
59 Cox proportional hazards models. In evidence triangulation, we assessed the potential
60 moderation-by-age-at-inflammatory-illness, associations relative to counterparts with other
61 similarly burdensome chronic illnesses, and the temporal ordering of conditions.

63 Findings

64 Both RA and axSpA were associated with mood and anxiety disorders and behavioural
65 syndromes. In evidence triangulation, associations with depression showed a decreasing age-
66 at-inflammatory-illness gradient in RA; the association between RA and depression was
67 stronger than that between other chronic illnesses and depression; excluding prevalent
68 depression attenuated the RA-depression association. RA showed consistent inverse
69 associations with schizophrenia and Alzheimer's disease.

71 Conclusions

72 Common aetiologies might be involved in increasing the risk of developing both RA and
73 depression. The consistent inverse associations between RA-schizophrenia and RA-
74 Alzheimer's disease suggest that at least part of these associations might also be a consequence
75 of shared aetiologies, as well as potential medication effects.

77 Clinical implications

78 People with autoimmune arthritides are more likely to experience mood and anxiety disorders,
79 even relative to counterparts with other similarly burdensome chronic illnesses.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- It remains incompletely understood whether the associations between inflammatory illnesses and mental disorders are predominantly a consequence of the burden of the former, or whether common causes might influence the susceptibility to both.

WHAT THIS STUDY ADDS

- Evidence triangulation suggests that common aetiologies might be involved in increasing the risk of developing both rheumatoid arthritis and depression.
- Evidence triangulations suggest that at least part of the rheumatoid arthritis-schizophrenia and rheumatoid arthritis-Alzheimer's disease associations might be a consequence of shared aetiologies or potential medication effects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Concerted efforts to better recognize and actively address neuropsychiatric conditions in people with inflammatory illnesses, are imperative.
- Disentangling the potential mechanisms responsible for the detected associations warrants further research efforts involving other data modalities and analytical approaches.

Background

There are cross-sectional associations between a pro-inflammatory state and several mental health conditions, most notably depression^[1,2] and psychosis^[3-5]. Longitudinal and genetic epidemiology studies; however, show broadly weak and inconsistent associations between inflammatory markers and mental health outcomes.^[6-9]

Rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA) are autoimmune illnesses, characterized by chronic inflammation in the musculoskeletal system, and differentially associated with specific mental disorders. In particular, while both RA and axSpA demonstrate substantial comorbidity with depression and anxiety^[10-13], these inflammatory illnesses show broadly consistent inverse associations with psychosis^[14,15]. However, it remains incompletely understood whether the associations between autoimmune arthritides and mental disorders are predominantly the consequence of the burden of the former, or whether common causes might influence the susceptibility to both.

In the present study, we considered psychiatric morbidity in people with autoimmune arthritides as a potential clinical model of inflammatory mechanisms in mental disorders. We hypothesized that two –contrasting but not mutually exclusive– primary mechanisms might explain the associations between inflammatory illnesses and mental disorders. One option is that, depression and other mental disorders might be the consequence of processes characterizing inflammatory illnesses, both in terms of chronic inflammation and the psychosocial burden associated with living with a chronic health condition and its treatment (i.e., burden of disease hypothesis). The second option is that a shared set of causal elements, such as genetic propensity and early life adversity, might influence the susceptibility to both inflammatory illnesses and depression and other mental disorders (i.e., shared aetiology hypothesis). This study was designed to investigate which of these mechanisms is dominant.

Objective

We used Czech national register-based data to investigate the associations between RA or axSpA and a wide range of mental disorders, including some that have been understudied so far. Then, we performed evidence triangulation by asking a set of alternative questions, answers to which, taken together, would lend support for either the burden of disease hypothesis or shared aetiology hypothesis. These questions and the rationale behind them were:

1. Are associations between RA or axSpA and mental disorders moderated by age at inflammatory illness?

A higher genetic burden for both oligogenic and common polygenic conditions often leads to a younger age of onset. Therefore, considering earlier age of onset as a proxy for higher genetic loading for the inflammatory illnesses, we hypothesized that if genetics was involved in the aetiologies of both, then the associations between inflammatory illnesses and mental disorders would be stronger in younger ages at inflammatory illnesses diagnoses.

2. Are associations between RA or axSpA and mental disorders comparable with those between other chronic illnesses and mental disorders?

We hypothesized that if the associations between inflammatory illnesses and mental disorders were not fully explicable by the burden of the former, then the associations would be stronger in people with inflammatory illnesses compared with people who had other chronic illnesses with the propensity to exhibit a similar burden.

3. Do the associations between RA or axSpA and mental disorders strengthen by excluding pre-existing mental disorders?

A shared aetiology would likely lead to more contemporaneous onset of inflammatory illnesses and mental disorders: mental disorders should thus not strictly follow inflammatory illnesses. On the contrary, this would be the case if burden of disease was predominantly responsible for psychiatric morbidity. We therefore hypothesized that if the associations between inflammatory illnesses and mental disorders were a consequence of burden of the former, then the associations would be stronger when only considering incident cases of mental disorders compared with analysis involving both incident and prevalent cases.

Methods

Data

We utilized individual-level, de-identified data from the Czech nation-wide inpatient services and mortality registers, covering the period from 1st January 1994 (the earliest available for the former) to 31st December 2017. The registers cover virtually the entire Czech population (approximately 10.7 million inhabitants). Linkage of registers is possible by the means of unique identifier assigned at birth. The registers are maintained by the state-funded Institute of Health Information and Statistics (IHIS), which granted access to complete data to the National Institute of Mental Health (NIMH).

The inpatient services register comprises of records created from information collected by health professionals using a standard form, following each discharge from virtually all Czech inpatient health-care settings, and includes day cases (i.e., admission and discharge on the same day). The English translation of the form is provided elsewhere.^[16] Basic clinical and socio-demographic characteristics are collected, including the dates of admission and discharge, the primary and, if applicable, secondary diagnoses coded according to the International Classification of Diseases, 10th Revision (ICD-10), age, sex, and region of residence. The mortality register consists of information based on death certificates that are routinely completed by physicians for all deaths occurring in Czechia. The date of death, cause(a) of death coded per ICD-10, and basic socio-demographic characteristics, including age at death and sex, are recorded.

From the initial 56,229,563 records, in line with our previous studies^[17,18], we excluded (1) records with missing information on key variables (admission and discharge date, primary diagnosis, sex, age, and region of residence) or incorrect (i.e., non-existent) dates (n = 34,761), (2) all records of individuals who have more than one date of death available or have hospitalizations following the date of death (n = 283,330), and (3) all records where a hospitalization began before the end of a previous one or where two hospitalizations began at the same time but ended at different ones (i.e., overlapping hospitalizations; n = 661,255). We used the first two criteria to remove records affected by administrative and/or technical errors, while the third criterion was to limit the risk of severe identification problems (negative time-to-events).

Exposures

We identified individuals aged 18 or more years who had RA (ICD-10 codes M05, M060, M062-M064 or M068-M069) or axSpA (ICD-10 codes M45 or M468-M469) listed as either the primary or secondary diagnoses in the period from 1st January 1999 to 31st December 2012. The cohort of individuals with RA or axSpA consisted of individuals having any the above

ICD-10 codes in the examined period. When an individual had multiple occurrences of the given code, we considered the first instance in the above period as the index record.

Matching

We matched individuals with either RA or axSpA with five counterparts who did not have these health conditions recorded up-to that point. We used exact matching on age, sex and discharge month and discharge year at index record. We used matching on sex and age because we considered them as important confounders, and matching on discharge month and discharge year to ensure that the individuals would have a comparable follow-up period and to control for possible calendar and cohort effects. We were able to match every individual.

Outcomes

We investigated the occurrence of mental disorders, listed as either the primary or secondary diagnoses recorded in the period of five or more years following the index record. We considered six diagnostic groups of mental disorders per ICD-10, consisting of organic disorders (F0, G20 and G30), substance use disorders (F1), psychotic disorders (F2), mood disorders (F3), anxiety disorders (F4), and behavioural syndromes associated with physiological disturbances and physical factors (e.g., eating and sleep disorders; F5). We also investigated nine closely-related and specific mental disorders per ICD-10, including Alzheimer's disease (F00 or G30), alcohol use disorders (F10), drug use disorders (F11-F19), schizophrenia (F20), bipolar disorder (F31), depression (F32-F33), moderate to severe depression (F321-F323 or F331-F333), other anxiety disorders (F41), reaction to severe stress, and adjustment disorders (F43), somatoform disorders (F45), and other neurotic disorders (F48). We investigated the occurrence of each of the mental disorders separately. We did not investigate psychiatric multimorbidity.

Evidence triangulation

Are associations between RA or axSpA and mental disorders moderated by age at inflammatory illness?

To test for this, we fitted models stratified per age recorded on the index record for RA or axSpA: 40 years or less, 41 to 59 years, and 60 years or more.

Are associations between RA or axSpA and mental disorders comparable with those between other chronic illnesses and mental disorders?

To test for this, we matched individuals with an inflammatory illness with up-to five counterparts with other chronic illnesses. We considered –per ICD-10 codes– chronic ischemic heart disease (I25), heart failure (I50), type 2 diabetes mellitus (E11), chronic obstructive pulmonary disease (J41-J44), asthma (J45), chronic kidney disease (N03, N11 or N18-N19), endometriosis (N80), non-alcoholic fatty liver disease (K760), epilepsy (G40-G41), and Parkinson's disease (G20-G22). We selected these illnesses because they are common, not customarily considered to be autoimmune inflammatory illnesses (even though autoimmune or inflammatory mechanisms may be partially involved in their physiopathology), and are also associated with substantial burden of disease (direct and psycho-social). To avoid overlap, we excluded individuals with the studied inflammatory illnesses who had any of the other chronic illnesses recorded five or more years before their index record. We used exact matching on age, sex and discharge month and discharge year at index record. Two individuals with RA could not be matched with any counterpart. To partially control for potential heterogeneity in disease severities, we further adjusted for the number of inpatient admissions in the period of five years before the index record.

Do the associations between RA or axSpA and mental disorders strengthen by excluding pre-existing mental disorders?

To test for this, we excluded individuals having been diagnosed with a mental disorder five or more years (i.e., wash-out period) prior to the index record for a given inflammatory illness, established separately for each studied psychiatric outcome. See Supplementary Figure 1 for differences compared with the main analysis.

Statistical analysis

We used stratified Cox proportional hazards models to investigate the associations between inflammatory illnesses and mental disorders. Each stratum consisted of one individual with the respective inflammatory illnesses and their exactly-matched, unexposed counterparts. Stratified Cox proportional hazards models involve comparisons within each stratum, allowing to control for the characteristics used in matching.^[19] We considered the outcome as the occurrence of a mental disorder between the index record and 31st December 2017. Individuals who did not experience the outcome or died during the follow-up period were censored. The underlying time-scale was in years following the discharge from index hospitalization. The results were expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). We examined whether the proportionality assumption was fulfilled using Schoenfeld residuals. In some cases, this assumption was violated; thus, HRs must be interpreted as weighted averages of the time-varying HRs over the entire follow-up period.^[20] We refrained from using null-hypothesis significance tests. All analyses were conducted in R statistical programming language (version 4.2.2)^[21], using the library *survival* (version 3.5-5).

Patient and public involvement

Patients or members of the public did not participate in designing or conducting this study, as well as in the interpretation of the results and writing of the manuscript.

Findings

The number of individuals in the RA cohort was 322,158 (exposed = 53,693 and unexposed = 268,465; mean age = 61.82; 76.08% females), whereas the number of individuals in the axSpA cohort was 56,148 (exposed = 9,358 and unexposed = 46,790; mean age = 53.56; 37.79% females). The detailed results are provided in Table 1.

Associations between RA or axSpA and mental disorders

Compared with matched counterparts, people with RA demonstrated an association with organic disorders, mood disorders, including depression, anxiety disorders, and behavioural syndromes. In contrast to these, we detected an inverse association between RA and psychotic disorders, including schizophrenia, as well as Alzheimer's disease. For substance use disorders, the results were consistent with a null effect.

People with axSpA demonstrated an association with mood disorders, including depression, anxiety disorders, and behavioural syndromes. AxSpA was inversely associated with schizophrenia. For organic disorders, including Alzheimer's disease, substance use disorders, and psychotic disorders, the results were consistent with a null effect. The detailed results are provided in Figure 1 and Supplementary Table 1-2.

Evidence triangulation

Are associations between RA or axSpA and mental disorders moderated by age at inflammatory illness?

RA was associated with mood disorders, including depression, regardless of age on the index record, with the strongest associations in those aged 40 years or less, followed by those aged 41 to 59 and 60 years or more. All RA age groups were also associated with anxiety disorders, but with a less clear age gradient. The youngest RA age group and those who were aged 41 to 59 years were associated with behavioural syndromes; however, individuals aged 60 years or more demonstrated null effects. We detected an inverse association between RA groups aged 41 to 59 and 60 years or more and psychotic disorders, including schizophrenia; however, the youngest age group demonstrated null effects. In those with RA aged 41 to 59, we detected an association with organic disorders, but the other two RA age groups displayed null effects. All three RA age groups demonstrated null effects for substance use disorders.

We detected that axSpA was associated with mood disorders, including depression, regardless of age on the index record, with the strength of associations decreasing from the youngest to the oldest axSpA age group. The strength of associations between axSpA and anxiety disorders was increasing from the youngest to the oldest axSpA age group. People with axSpA demonstrated null effects for organic disorders, substance use disorders, and psychotic disorders regardless of their age on the index record. The detailed results are provided in Table 2 and Supplementary Table 3-4.

Are associations between RA or axSpA and mental disorders comparable with those between other chronic illnesses and mental disorders?

Relative to matched counterparts with other chronic illnesses, individuals with RA demonstrated associations with mood disorders, including depression, and anxiety disorders. We detected inverse associations between RA and organic disorders, including Alzheimer's disease, substance use disorders, and psychotic disorders, including schizophrenia. The results for behavioural syndromes were consistent with a null effect.

People with axSpA demonstrated associations with mood disorders, including depression, and behavioural syndromes, when compared with their matched counterparts with other chronic illnesses. Conversely, we detected inverse associations between axSpA and organic disorders (but not Alzheimer's disease in particular), substance use disorders, and psychotic disorders, including schizophrenia. The results for anxiety disorders were consistent with a null effect. The detailed results are provided in Figure 2 and Supplementary Table 5-7.

Do the associations between RA or axSpA and mental disorders strengthen by excluding pre-existing mental disorders?

We detected weaker associations between RA and incident anxiety disorders and behavioural syndromes compared with analyses including also prevalent cases of these mental disorders. Considering only incident cases of organic disorders and psychotic disorders, including Alzheimer's disease and schizophrenia in particular, led to more pronounced inverse associations between RA and these. The null effects between RA and incident cases of mood disorders, including depression, diverged from the analyses including also prevalent cases of these mental disorders.

We demonstrated attenuated associations between axSpA and incident mood disorders, anxiety disorders, and behavioural syndromes compared with analyses including also prevalent cases of these mental disorders. Considering only incident cases of organic disorders and psychotic

disorders, including Alzheimer's disease and schizophrenia in particular, led to null effects, which were consistent with analyses including also prevalent cases of these mental disorders. The detailed results are provided in Figure 3 and Supplementary Table 8-10.

Discussion

Principal findings

We used Czech national register-based data to investigate the associations between RA or axSpA and a wide range of mental disorders, considering them to be a potential clinical model of inflammatory mechanisms in mental disorders. We demonstrated that both inflammatory illnesses were associated with mood disorders, anxiety disorders, and behavioural syndromes. Our evidence triangulation showed that associations with mood disorders, and depression in particular, showed a strong decreasing age-at-inflammatory-illness gradient in both inflammatory illnesses; compared with counterparts who had other chronic illnesses, people with RA or axSpA demonstrated associations with mood disorders, including depression; compared with analyses including also prevalent cases of depression, the association between axSpA and incident cases of depression attenuated, whereas the association between RA and incident depression was consistent with a null effect, this being suggestive of RA not strictly temporally preceding depression. Furthermore, we detected consistent inverse associations between RA-schizophrenia and RA-Alzheimer's disease.

Comparison with existing evidence and potential mechanisms

For tractability, we provide in-depth discussion for only a subset of detected associations that we consider to be of the highest relevance and importance.

RA and depression

The association we detected between RA and depression is consistent with findings from register-based studies from Sweden^[22], Taiwan^[23], and the United Kingdom^[24]. Stronger associations in younger individuals with RA, also aligning with a study from the United Kingdom^[24], no evidence of RA strictly temporally preceding depression, and stronger association between RA and depression than between other chronic illnesses and depression, might support the notion of a shared aetiology. In RA, the interleukin 6 pathway is involved in inflammatory processes^[25] and elevated C-reactive protein levels reflect disease activity^[26], and meta-analytical evidence shows associations between these markers and depression.^[1,27,28] Importantly, RA and depression share several immune alterations^[29], and the involvement of these inflammatory markers in both RA and depression might be the consequence of such alterations. This would then further align with the possibility of shared causal elements.^[29]

However, two Mendelian randomization studies failed to detect any evidence of causality between RA and depression^[30,31], while another Mendelian randomization study showed that inflammatory cytokines may not be the mediating mechanism between RA and depression^[32]. The lack of causality demonstrated in these studies should be nonetheless interpreted cautiously, considering that Mendelian randomization is highly sensitive to genetic instrument strength. While the genome-wide association studies of depression had considerably large samples, those for inflammatory illnesses and inflammatory cytokines involved much smaller sample sizes, and might have therefore lacked the power to detect an effect.^[30-32] However, these Mendelian randomization findings do point at an alternative primary explanation for the presence of depression in people with RA.

RA onset earlier in life might translate in more severe, active, and potentially treatment-resistant forms of the disease. This in turn may cause more disability and reduced quality of life, and then contribute to developing depression, even in the absence of a common biological cause. This alternative explanation, however, is not supported by our findings, which show that excluding prevalent cases of depression nullifies the RA-depression association.

RA and schizophrenia

We demonstrated a consistent inverse association between RA and schizophrenia. This inverse association between RA and schizophrenia has been shown previously in register-based studies from Sweden^[33], Denmark^[34], and Taiwan^[35]. Explanations for these inverse associations might include the potentially prophylactic effect of antipsychotic medication on RA onset later in life^[36], or the potential involvement of RA treatments in reducing the risk of schizophrenia. For instance, methotrexate had a prominent position in the Czech as well as international clinical guidelines for RA over the course of this study, while this medication is generally not indicated for treating axSpA. A small, early-phase trial of methotrexate indicated anti-disease activity potential in schizophrenia.^[37] Thus, its differential use in the treatment of RA and axSpA might be one of the reasons the two patient groups demonstrated differential risks for psychoses, including schizophrenia.

An alternative explanation that involves underreporting or underdiagnosis, cannot be discounted, given that people with schizophrenia are well known for having reluctance or difficulties accessing or engaging with health-care systems. This is broadly supported by the findings of a Swedish register-based study that showed decreased risk of RA in people with schizophrenia, but risks consistent with a null effect in their children, siblings, or parents.^[33] However, the same study also demonstrated a decreased risk of seronegative RA in siblings and children of people with schizophrenia: this would thus suggest that part of these associations can also be due to shared common biological causes.^[33]

RA and Alzheimer's disease

We detected consistent inverse association between RA and Alzheimer's disease. A similar inverse association was demonstrated in register-based studies from Taiwan^[38] and the United Kingdom^[39]. A Mendelian randomization study demonstrated a decreased risk between genetically predicted RA and Alzheimer's disease; however, the results were not robust across all analyses.^[40] The same study, then, demonstrated an elevated risk for Alzheimer's disease using register-based data from the United Kingdom.^[40]

The lack of consistency in evidence largely precludes us from proposing potential mechanisms responsible for these associations; however, a multi-national multi-database case-control study demonstrated a lower risk of –broadly defined– dementia in people who previously used methotrexate^[41], a medication which has been used widely to treat RA over the studied period.

Methodological considerations

Strengths of this study include using national, routinely collected, standardised health and mortality data. This supported the analysis of usefully precise matched cohorts of people with and without inflammatory illnesses and their psychiatric outcomes. Furthermore, the follow-up period for most individuals was such that we could capture the outcomes over a substantially long period.

This study has some limitations. First, we are aware that a proportion of the studied inflammatory illnesses and mental disorders will be diagnosed and treated in community

settings (i.e., primary and outpatient care). It is possible –given that this study is based on inpatient services data– that we might be biased towards the more severe end of the inflammatory and psychiatric condition spectrum. However, it is important to remark that the inpatient services data we have been using cover any presenting complaints at the time of the admission, and are not limited to admissions due to inflammatory and psychiatric conditions, implying that the bias might be generally towards people with increased inpatient care needs (i.e., informative presence bias^[42]), and not specifically towards our conditions of interest. Consequently, the bias would not impact the internal validity of the study, but rather the potential generalisability to other healthcare settings. Second, we did not have information on several important socio-demographic, behavioural, and clinical characteristics; thus, we cannot rule out that part of the observed associations is due to residual confounding. In particular, we had no information on results of biochemical examinations, disease activity, and disease severity, all of which are likely to be strongly associated with the outcomes. Relatedly, in analyses involving comparisons with people who had other chronic illnesses, we could not match on the precise levels of disease severity. Third, the matched counterparts without autoimmune arthritides were retrieved from the inpatient care register, and they likely had elevated levels of inflammation themselves, considering that inflammation is a hallmark of many health conditions. Consequently, our results might have underestimated the true effect of having an inflammatory illness on psychiatric outcomes. Fourth, we had neither data on genetics nor data on psychosocial functioning to directly study their potential involvement in associations between the inflammatory illnesses and mental disorders. Fifth, to date, there has been no formal evaluation of all diagnoses used in this study, and we cannot rule out the possibility of under-registration and/or misclassification of diagnoses. Sixth, in our age-stratified models, we used information recoded on the index record; however, this can differ from both the first-ever diagnosis age and the symptoms onset age for a given individual. Last, the number of outcomes in certain analyses –particularly age-stratified ones– was low, resulting in large uncertainty about the effects.

Clinical implications

This study was not designed to ascertain the specific biological mechanisms underpinning the associations between inflammation and mental disorders. However, our findings might have implications for clinical practice. They suggest that people with either RA or axSpA are more likely to experience certain groups of mental disorders, particularly mood disorders, even relative to counterparts who have other chronic illnesses with similar burden. Despite the presence of substantial psychiatric morbidity in these people, high-profile international guidelines on management of RA and axSpA contain no^[43] or only perfunctory mention^[44,45] of the importance of assessing and treating mental disorders in people with these inflammatory illnesses.

Thus, concerted efforts to better recognize and actively address neuropsychiatric conditions in people with either RA or axSpA, are imperative. This could entail having a multidisciplinary approach to inflammatory illnesses or incorporating psychiatry professionals/assessments as part of the clinical pathway, among others. Providing such holistic care for inflammatory and psychiatric conditions has the potential to improve outcomes in both health domains.

Data availability statement

Due to its sensitive nature, the data cannot be published or shared with external subjects without permission from the Czech Institute of Health Information and Statistics. The full analytical code of the study is available at a dedicated GitHub repository: <https://github.com/tmfmnk/Autoimmune-arthritides-as-a-model-of-inflammatory->

mechanisms-in-mental-disorders. TF and KM had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics statement

Patient consent for publication

Not applicable.

Ethics approval

This study was approved by the Ethics Committee of the National Institute of Mental Health (approval number 144/20).

Authors contributions

TF initiated and designed the study, performed the statistical analysis and led the writing of the manuscript. KM contributed to designing the study, statistical analysis, and interpretation of results, performed the code review, and provided critical revisions to the manuscript. PM contributed to designing the study and interpretation of results, and provided critical revisions to the manuscript. MFL contributed to designing the study and interpretation of results, and provided critical revisions to the manuscript. MO contributed to designing the study and provided critical revisions to the manuscript. KP contributed to designing the study and provided critical revisions to the manuscript. PW contributed to designing the study and interpretation of results, and provided critical revisions to the manuscript. EFO contributed to designing the study, the literature review and interpretation of results, and wrote a substantial part of the manuscript. PBJ contributed to designing the study, interpretation of results, and provided supervision and critical revisions to the manuscript. MH contributed to designing the study, the literature review and the interpretation of results, and provided critical revisions to the manuscript. All authors approved the decision to submit for publication. TF is the guarantor.

Conflict of interest statement

The authors have nothing to disclose.

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Table 1 Descriptive statistics of the cohorts

Characteristic	Cohort					
	Rheumatoid arthritis or axial spondyloarthritis		Rheumatoid arthritis		Axial spondyloarthritis	
	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed
Overall, n	311,345	62,269	268,465	53,693	46,790	9,358
Age, mean (SD)	60.68 (14.73)	60.68 (14.73)	61.82 (14.21)	61.82 (14.21)	53.56 (15.79)	53.56 (15.79)
Females, n (%)	219,875 (70.62)	43,975 (70.62)	204,260 (76.08)	40,852 (76.08)	17,680 (37.79)	3,536 (37.79)
Discharge year, median (IQR)	2006 (2002-2009)	2006 (2002-2009)	2006 (2002-2009)	2006 (2002-2009)	2007 (2003-2010)	2007 (2003-2010)
Discharge month median (IQR)	6 (4-10)	6 (4-10)	6 (4-10)	6 (4-10)	6 (3-10)	6 (3-10)

The results are expressed as absolute numbers (n), means with standard deviations (SD), and medians with interquartile ranges (IQR). We note that since each individual with an inflammatory illness was exactly-matched with five counterparts without the respective inflammatory illness, the distribution on each of the characteristics is identical between the groups.

Table 2 Associations between rheumatoid arthritis or axial spondyloarthritis and mental disorders, stratification by age recorded on the index record

Age group	Outcome	Cohort		
		Rheumatoid arthritis or axial spondyloarthritis	Rheumatoid arthritis	Axial spondyloarthritis
40 years or less	Organic disorders	1.15 (0.77; 1.71)	1.09 (0.67; 1.78)	NA
40 years or less	Alzheimer's disease	NA	NA	NA
40 years or less	Substance use disorders	0.98 (0.86; 1.12)	0.85 (0.72; 1.02)	0.91 (0.75; 1.10)
40 years or less	Alcohol use disorders	0.91 (0.77; 1.08)	0.77 (0.61; 0.96)	0.84 (0.66; 1.06)
40 years or less	Drug use disorders	1.14 (0.95; 1.36)	1.00 (0.80; 1.27)	1.12 (0.87; 1.46)
40 years or less	Psychotic disorders	1.05 (0.81; 1.36)	0.99 (0.71; 1.39)	0.79 (0.53; 1.17)
40 years or less	Schizophrenia	0.96 (0.68; 1.34)	0.95 (0.61; 1.47)	0.68 (0.42; 1.12)
40 years or less	Mood disorders	2.29 (1.93; 2.71)	2.35 (1.92; 2.88)	1.84 (1.36; 2.47)
40 years or less	Bipolar disorder	1.64 (1.01; 2.66)	1.76 (1.03; 3.02)	NA
40 years or less	Depression	2.44 (2.04; 2.93)	2.53 (2.03; 3.14)	1.99 (1.46; 2.72)
40 years or less	Moderate or severe depression	2.15 (1.63; 2.82)	2.32 (1.64; 3.29)	2.65 (1.68; 4.20)
40 years or less	Anxiety disorders	2.02 (1.77; 2.32)	1.81 (1.54; 2.12)	1.60 (1.27; 2.01)
40 years or less	Other anxiety disorders	2.28 (1.83; 2.84)	1.89 (1.47; 2.43)	1.56 (1.06; 2.32)
40 years or less	Reaction to severe stress	1.62 (1.31; 2.01)	1.31 (1.00; 1.70)	1.25 (0.89; 1.74)
40 years or less	Somatoform disorders	3.20 (2.12; 4.82)	3.20 (1.91; 5.34)	3.98 (2.06; 7.67)
40 years or less	Other neurotic disorders	3.02 (2.12; 4.31)	3.13 (2.06; 4.76)	2.60 (1.42; 4.77)
40 years or less	Behavioural syndromes	2.52 (1.63; 3.92)	2.02 (1.15; 3.56)	3.53 (1.82; 6.84)
41 to 59 years	Organic disorders	1.47 (1.32; 1.64)	1.46 (1.30; 1.64)	1.18 (0.93; 1.51)
41 to 59 years	Alzheimer's disease	1.35 (0.97; 1.90)	1.37 (0.94; 1.99)	NA
41 to 59 years	Substance use disorders	1.05 (0.98; 1.13)	1.01 (0.93; 1.10)	0.97 (0.84; 1.13)
41 to 59 years	Alcohol use disorders	0.83 (0.75; 0.92)	0.80 (0.71; 0.90)	0.83 (0.69; 1.00)
41 to 59 years	Drug use disorders	1.38 (1.24; 1.53)	1.28 (1.14; 1.44)	1.30 (1.05; 1.62)
41 to 59 years	Psychotic disorders	0.64 (0.54; 0.78)	0.66 (0.54; 0.82)	0.69 (0.46; 1.04)
41 to 59 years	Schizophrenia	0.55 (0.42; 0.72)	0.51 (0.37; 0.69)	0.57 (0.33; 0.99)
41 to 59 years	Mood disorders	1.67 (1.54; 1.81)	1.65 (1.51; 1.80)	1.49 (1.22; 1.81)
41 to 59 years	Bipolar disorder	1.19 (0.91; 1.56)	1.32 (0.99; 1.76)	1.03 (0.53; 1.98)
41 to 59 years	Depression	1.71 (1.57; 1.86)	1.67 (1.52; 1.83)	1.50 (1.22; 1.84)

41 to 59 years	Moderate or severe depression	1.49 (1.29; 1.72)	1.49 (1.28; 1.74)	1.46 (1.04; 2.04)
41 to 59 years	Anxiety disorders	1.95 (1.81; 2.10)	1.84 (1.70; 2.00)	1.87 (1.56; 2.23)
41 to 59 years	Other anxiety disorders	1.97 (1.77; 2.19)	1.87 (1.66; 2.10)	1.82 (1.40; 2.36)
41 to 59 years	Reaction to severe stress	1.61 (1.39; 1.86)	1.47 (1.25; 1.73)	1.86 (1.37; 2.52)
41 to 59 years	Somatoform disorders	2.31 (1.84; 2.90)	2.15 (1.68; 2.75)	2.53 (1.49; 4.30)
41 to 59 years	Other neurotic disorders	2.64 (2.26; 3.08)	2.52 (2.13; 2.97)	3.03 (2.06; 4.46)
41 to 59 years	Behavioural syndromes	2.31 (1.70; 3.15)	2.29 (1.63; 3.22)	3.03 (1.52; 6.05)
60 years or more	Organic disorders	1.05 (1.00; 1.09)	1.02 (0.97; 1.07)	1.10 (0.96; 1.26)
60 years or more	Alzheimer's disease	0.86 (0.78; 0.95)	0.84 (0.76; 0.92)	0.90 (0.65; 1.25)
60 years or more	Substance use disorders	1.04 (0.93; 1.15)	1.01 (0.90; 1.13)	1.05 (0.81; 1.37)
60 years or more	Alcohol use disorders	0.88 (0.75; 1.04)	0.84 (0.71; 1.00)	0.73 (0.49; 1.10)
60 years or more	Drug use disorders	1.16 (1.01; 1.32)	1.16 (1.00; 1.34)	1.49 (1.06; 2.10)
60 years or more	Psychotic disorders	0.64 (0.52; 0.80)	0.68 (0.54; 0.86)	0.99 (0.51; 1.90)
60 years or more	Schizophrenia	0.42 (0.29; 0.61)	0.40 (0.27; 0.60)	NA
60 years or more	Mood disorders	1.35 (1.24; 1.46)	1.32 (1.21; 1.43)	1.35 (1.02; 1.78)
60 years or more	Bipolar disorder	0.90 (0.63; 1.29)	0.93 (0.64; 1.33)	NA
60 years or more	Depression	1.39 (1.28; 1.51)	1.33 (1.22; 1.46)	1.44 (1.08; 1.91)
60 years or more	Moderate or severe depression	1.25 (1.07; 1.46)	1.20 (1.02; 1.40)	1.05 (0.60; 1.82)
60 years or more	Anxiety disorders	1.69 (1.57; 1.83)	1.55 (1.43; 1.68)	2.75 (2.13; 3.54)
60 years or more	Other anxiety disorders	1.58 (1.41; 1.77)	1.44 (1.28; 1.62)	2.77 (1.92; 4.00)
60 years or more	Reaction to severe stress	1.65 (1.37; 1.98)	1.37 (1.14; 1.66)	2.33 (1.35; 4.02)
60 years or more	Somatoform disorders	1.52 (1.19; 1.95)	1.39 (1.08; 1.79)	NA
60 years or more	Other neurotic disorders	2.00 (1.75; 2.29)	1.91 (1.66; 2.20)	3.53 (2.17; 5.77)
60 years or more	Behavioural syndromes	1.76 (1.26; 2.46)	1.43 (1.00; 2.04)	NA

NA denotes situations when the number of events in either the exposed or unexposed group was ≤ 10 . To avoid excessive uncertainty, we refrained from analysing these categories. The results are expressed as hazard ratios with 95% confidence intervals. Individuals with rheumatoid arthritis or axial spondyloarthritis were compared with counterparts matched on age, sex, month and year at the index record. Both incident and prevalent cases of mental disorders were considered.

Figure 1 Associations between rheumatoid arthritis or axial spondyloarthritis and mental disorders

The results are expressed as hazard ratios with 95% confidence intervals. Individuals with rheumatoid arthritis or axial spondyloarthritis were compared with counterparts matched on age, sex, month and year at the index record. Both incident and prevalent cases of mental disorders were considered.

Figure 2 Associations between rheumatoid arthritis or axial spondyloarthritis and mental disorders, comparison with matched counterparts with other chronic illnesses

The results are expressed as hazard ratios with 95% confidence intervals. Individuals with rheumatoid arthritis or axial spondyloarthritis without any of the other chronic illnesses were compared with matched counterparts who had at least one of the considered chronic illnesses. Matching was performed on age, sex, month and year at the index record. We adjusted for the number of hospitalizations in the period of five years before the index record. Both incident and prevalent cases of mental disorders were considered.

Figure 3 Associations between rheumatoid arthritis or axial spondyloarthritis and mental disorders, excluding people with pre-existing mental disorders

The results are expressed as hazard ratios with 95% confidence intervals. Individuals with rheumatoid arthritis or axial spondyloarthritis were compared with counterparts matched on age, sex, month and year at the index record. Only incident cases of mental disorders were considered.