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ADULT MENTAL HEALTH

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

Tomáš Formánek ,[1,2,3] Karolína Mladá,[2,4] Pavel Mohr,[5,6] Mao Fong Lim,[1,7] Marta Olejárová,[8,9] Karel Pavelka,[8,9] Petr Winkler,[2,10,11] Emanuele Felice Osimo ,[1,7,12] Peter B Jones ,[1,7] Markéta Hušáková[8,9]

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For numbered affiliations see end of article.

Correspondence to
Dr Tomáš Formánek, University of Cambridge Department of Psychiatry, Cambridge, CB2 0SZ, UK; tf363@cam.ac.uk

EFO, PBJ and MHšá are joint senior authors.

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ABSTRACT

Background Rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA) are autoimmune illnesses characterised by chronic inflammation demonstrating differential associations with psychiatric conditions.

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

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

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

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

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

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 triangulation suggests 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 recognise and actively address neuropsychiatric conditions in people with inflammatory illnesses are imperative.

⇒ Disentangling the potential mechanisms responsible for the identified associations warrants further research efforts involving other data modalities and analytical approaches.

BACKGROUND

There are cross-sectional associations between a proinflammatory 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 characterised 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 hypothesised 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 characterising inflammatory illnesses, both in terms of chronic inflammation and the psychosocial burden associated with living with a chronic health condition and its treatment (ie, 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 (ie, 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. We then performed evidence triangulation by asking a set of alternative questions, answers to which, taken together, would lend support to either the burden of disease hypothesis or the shared aetiology hypothesis. The questions and the rationale behind them are the following:

1. Are the 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 hypothesised that if genetics were involved in the aetiologies of both, then the associations between inflammatory illnesses and mental disorders would be stronger in younger ages at inflammatory illness diagnoses.
2. Are the associations between RA or axSpA and mental disorders comparable with those between other chronic illnesses and mental disorders?
   We hypothesised 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 the burden of disease was predominantly responsible for psychiatric morbidity. We therefore hypothesised that if the associations between inflammatory illnesses and mental disorders were a consequence of the 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 used individual-level, de-identified data from the Czech nationwide inpatient services and mortality registers, covering the period from 1 January 1994 (the earliest available for the former) to 31 December 2017. The registers cover virtually the entire Czech population (approximately 10.7 million inhabitants). Linkage of registers is possible by means of a unique identifier assigned at birth. The registers are maintained by the state-funded Institute of Health Information and Statistics, which granted access to complete data to the National Institute of Mental Health.

The inpatient services register comprises records created from the information collected by health professionals using a standard form, following each discharge from virtually all Czech inpatient healthcare settings, and includes day cases (ie, admission and discharge on the same day). The English translation of the form is provided elsewhere.[16] Basic clinical and sociodemographic 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, which are routinely completed by physicians for all deaths occurring in Czechia. The date of death, the cause(s) of death coded per ICD-10 and the basic sociodemographic 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 (ie, non-existent) dates (n=34 761); (2) all records of individuals who have more than one date of death available or have hospitalisations following the date of death (n=283 330); and (3) all records where a hospitalisation began before the end of a previous one or where two hospitalisations began at the same time but ended at different times (ie, overlapping hospitalisations; 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 code M05, M060, M062–M064 or M068–M069) or axSpA (ICD-10 code M45 or M468–M469) listed as either the primary or the secondary diagnoses in the period from 1 January 1999 to 31 December 2012. The cohort of individuals with RA or axSpA consisted of individuals having any of the above ICD-10 codes during 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 on the 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 (both incident and prevalent cases), listed as either the primary or the secondary diagnoses recorded in the period of 5 or more years following the index record. We considered six diagnostic groups of mental disorders per ICD-10, consisting of organic disorders (F0, G20 or G30), substance use disorders (F1), psychotic disorders (F2), mood disorders (F3), anxiety disorders (F4) and behavioural syndromes associated with physiological disturbances and physical factors (eg, eating and sleep disorders; F5). We also investigated 11 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 the 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 below, 41–59 years and 60 years or above.

Are the 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 ischaemic 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 a substantial burden of disease (direct and psychosocial). To avoid overlap, we excluded individuals with the studied inflammatory illnesses who had any of the other chronic illnesses recorded 5 or more years before their index record. We used exact matching on age, sex, discharge month and discharge year on the 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 5 years before the index record. See online supplemental figure 1 for differences compared with the main analysis.

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

To test for this, we excluded individuals who have been diagnosed with a mental disorder 5 or more years (ie, washout period) prior to the index record for a given inflammatory illness, established separately for each studied psychiatric outcome. See online supplemental 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 31 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 discharge from index hospitalisation. The results were expressed as HRs with 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 (V.4.2.2)[21] using the library *survival* (V.3.5-5).

Patient and public involvement

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

FINDINGS

The number of individuals in the RA cohort was 322 158 (exposed=53 693, unexposed=268 465; mean age=61.82; 76.08% female), whereas the number of individuals in the axSpA cohort was 56 148 (exposed=9358, unexposed=46 790;

Table 1 Descriptive statistics of the cohorts

	Cohort					
	Rheumatoid arthritis or axial spondyloarthritis		Rheumatoid arthritis		Axial spondyloarthritis	
Characteristics	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed
Overall, n	311 345	62 269	268 465	53 693	46 790	9358
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)
Female, n (%)	219 875 (70.62)	43 975 (70.62)	204 260 (76.08)	40 852 (76.08)	17 680 (37.79)	3536 (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 number (n), mean with SD and median with 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.

mean age=53.56; 37.79% female). 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 and mood disorders, including depression, anxiety disorders and behavioural syndromes. In contrast, 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. Detailed results are provided in figure 1 and online supplemental tables 1 and 2.

Evidence triangulation

Are the 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 below, followed by those aged 41–59 and those aged 60 years or above. All RA age groups were also associated with anxiety disorders, but with a less clear age gradient. The youngest RA age group and those aged 41–59 years were associated with behavioural syndromes; however, individuals aged 60 years or above demonstrated null effects. We detected an inverse association between RA groups aged 41–59 and 60 years or above and psychotic disorders, including schizophrenia; however, the youngest age group demonstrated null effects. In those with RA aged 41–59, we detected an association with organic disorders, while 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 increased 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. Detailed results are provided in table 2 and online supplemental tables 3 and 4.

Are the 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. Detailed results are provided in figure 2 and online supplemental tables 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 also including prevalent cases of these mental disorders. Detailed results are provided in figure 3 and online supplemental tables 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 the 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. Also, 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 and schizophrenia and between RA and Alzheimer's disease.

Comparison with existing evidence and potential mechanisms

For tractability, we provide indepth discussion for only a subset of detected associations that we consider to be of 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 UK.[24] The stronger associations in younger individuals with RA, also aligning with a study from the UK,[24] the lack of evidence of RA strictly temporally preceding depression and the stronger association between RA and depression compared with those between other chronic illnesses and

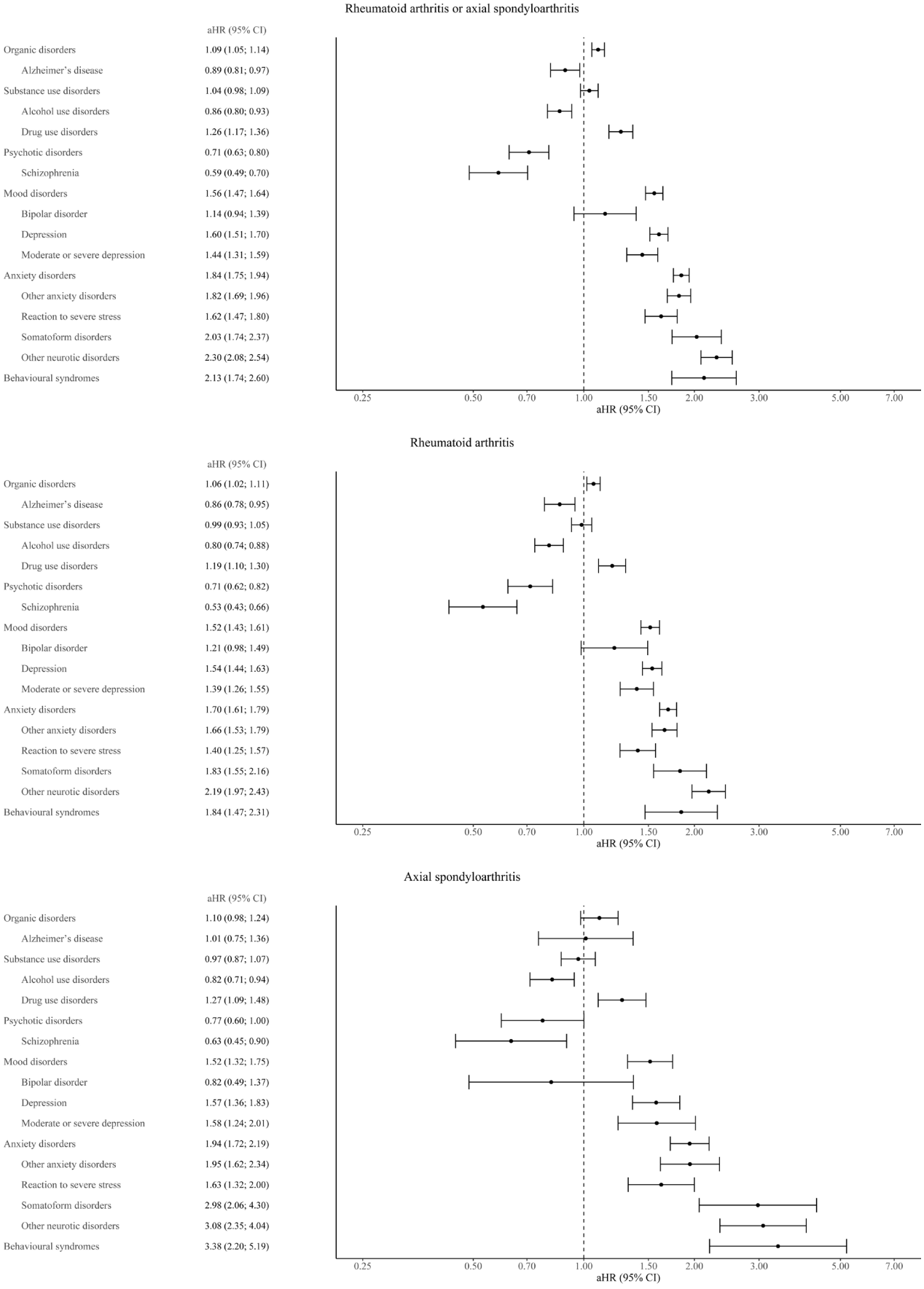

Figure 1 Associations between rheumatoid arthritis or axial spondyloarthritis and mental disorders. The results are expressed as adjusted HR (aHR) with 95% CI. Individuals with rheumatoid arthritis or axial spondyloarthritis were compared with counterparts matched on age, sex, month and year on the index record. Both incident and prevalent cases of mental disorders were considered.

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

		Cohort		
Age group (years)	**Outcome**	**Rheumatoid arthritis or axial spondyloarthritis**	**Rheumatoid arthritis**	**Axial spondyloarthritis**
40 or below	Organic disorders	1.15 (0.77, 1.71)	1.09 (0.67, 1.78)	NA
40 or below	Alzheimer's disease	NA	NA	NA
40 or below	Substance use disorders	0.98 (0.86, 1.12)	0.85 (0.72, 1.02)	0.91 (0.75, 1.10)
40 or below	Alcohol use disorders	0.91 (0.77, 1.08)	0.77 (0.61, 0.96)	0.84 (0.66, 1.06)
40 or below	Drug use disorders	1.14 (0.95, 1.36)	1.00 (0.80, 1.27)	1.12 (0.87, 1.46)
40 or below	Psychotic disorders	1.05 (0.81, 1.36)	0.99 (0.71, 1.39)	0.79 (0.53, 1.17)
40 or below	Schizophrenia	0.96 (0.68, 1.34)	0.95 (0.61, 1.47)	0.68 (0.42, 1.12)
40 or below	Mood disorders	2.29 (1.93, 2.71)	2.35 (1.92, 2.88)	1.84 (1.36, 2.47)
40 or below	Bipolar disorder	1.64 (1.01, 2.66)	1.76 (1.03, 3.02)	NA
40 or below	Depression	2.44 (2.04, 2.93)	2.53 (2.03, 3.14)	1.99 (1.46, 2.72)
40 or below	Moderate or severe depression	2.15 (1.63, 2.82)	2.32 (1.64, 3.29)	2.65 (1.68, 4.20)
40 or below	Anxiety disorders	2.02 (1.77, 2.32)	1.81 (1.54, 2.12)	1.60 (1.27, 2.01)
40 or below	Other anxiety disorders	2.28 (1.83, 2.84)	1.89 (1.47, 2.43)	1.56 (1.06, 2.32)
40 or below	Reaction to severe stress	1.62 (1.31, 2.01)	1.31 (1.00, 1.70)	1.25 (0.89, 1.74)
40 or below	Somatoform disorders	3.20 (2.12, 4.82)	3.20 (1.91, 5.34)	3.98 (2.06, 7.67)
40 or below	Other neurotic disorders	3.02 (2.12, 4.31)	3.13 (2.06, 4.76)	2.60 (1.42, 4.77)
40 or below	Behavioural syndromes	2.52 (1.63, 3.92)	2.02 (1.15, 3.56)	3.53 (1.82, 6.84)
41–59	Organic disorders	1.47 (1.32, 1.64)	1.46 (1.30, 1.64)	1.18 (0.93, 1.51)
41–59	Alzheimer's disease	1.35 (0.97, 1.90)	1.37 (0.94, 1.99)	NA
41–59	Substance use disorders	1.05 (0.98, 1.13)	1.01 (0.93, 1.10)	0.97 (0.84, 1.13)
41–59	Alcohol use disorders	0.83 (0.75, 0.92)	0.80 (0.71, 0.90)	0.83 (0.69, 1.00)
41–59	Drug use disorders	1.38 (1.24, 1.53)	1.28 (1.14, 1.44)	1.30 (1.05, 1.62)
41–59	Psychotic disorders	0.64 (0.54, 0.78)	0.66 (0.54, 0.82)	0.69 (0.46, 1.04)
41–59	Schizophrenia	0.55 (0.42, 0.72)	0.51 (0.37, 0.69)	0.57 (0.33, 0.99)
41–59	Mood disorders	1.67 (1.54, 1.81)	1.65 (1.51, 1.80)	1.49 (1.22, 1.81)
41–59	Bipolar disorder	1.19 (0.91, 1.56)	1.32 (0.99, 1.76)	1.03 (0.53, 1.98)
41–59	Depression	1.71 (1.57, 1.86)	1.67 (1.52, 1.83)	1.50 (1.22, 1.84)
41–59	Moderate or severe depression	1.49 (1.29, 1.72)	1.49 (1.28, 1.74)	1.46 (1.04, 2.04)
41–59	Anxiety disorders	1.95 (1.81, 2.10)	1.84 (1.70, 2.00)	1.87 (1.56, 2.23)
41–59	Other anxiety disorders	1.97 (1.77, 2.19)	1.87 (1.66, 2.10)	1.82 (1.40, 2.36)
41–59	Reaction to severe stress	1.61 (1.39, 1.86)	1.47 (1.25, 1.73)	1.86 (1.37, 2.52)
41–59	Somatoform disorders	2.31 (1.84, 2.90)	2.15 (1.68, 2.75)	2.53 (1.49, 4.30)
41–59	Other neurotic disorders	2.64 (2.26, 3.08)	2.52 (2.13, 2.97)	3.03 (2.06, 4.46)
41–59	Behavioural syndromes	2.31 (1.70, 3.15)	2.29 (1.63, 3.22)	3.03 (1.52, 6.05)
60 or above	Organic disorders	1.05 (1.00, 1.09)	1.02 (0.97, 1.07)	1.10 (0.96, 1.26)
60 or above	Alzheimer's disease	0.86 (0.78, 0.95)	0.84 (0.76, 0.92)	0.90 (0.65, 1.25)
60 or above	Substance use disorders	1.04 (0.93, 1.15)	1.01 (0.90, 1.13)	1.05 (0.81, 1.37)
60 or above	Alcohol use disorders	0.88 (0.75, 1.04)	0.84 (0.71, 1.00)	0.73 (0.49, 1.10)
60 or above	Drug use disorders	1.16 (1.01, 1.32)	1.16 (1.00, 1.34)	1.49 (1.06, 2.10)
60 or above	Psychotic disorders	0.64 (0.52, 0.80)	0.68 (0.54, 0.86)	0.99 (0.51, 1.90)
60 or above	Schizophrenia	0.42 (0.29, 0.61)	0.40 (0.27, 0.60)	NA
60 or above	Mood disorders	1.35 (1.24, 1.46)	1.32 (1.21, 1.43)	1.35 (1.02, 1.78)
60 or above	Bipolar disorder	0.90 (0.63, 1.29)	0.93 (0.64, 1.33)	NA
60 or above	Depression	1.39 (1.28, 1.51)	1.33 (1.22, 1.46)	1.44 (1.08, 1.91)
60 or above	Moderate or severe depression	1.25 (1.07, 1.46)	1.20 (1.02, 1.40)	1.05 (0.60, 1.82)
60 or above	Anxiety disorders	1.69 (1.57, 1.83)	1.55 (1.43, 1.68)	2.75 (2.13, 3.54)
60 or above	Other anxiety disorders	1.58 (1.41, 1.77)	1.44 (1.28, 1.62)	2.77 (1.92, 4.00)
60 or above	Reaction to severe stress	1.65 (1.37, 1.98)	1.37 (1.14, 1.66)	2.33 (1.35, 4.02)
60 or above	Somatoform disorders	1.52 (1.19, 1.95)	1.39 (1.08, 1.79)	NA
60 or above	Other neurotic disorders	2.00 (1.75, 2.29)	1.91 (1.66, 2.20)	3.53 (2.17, 5.77)
60 or above	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 the unexposed group was ≤10. To avoid excessive uncertainty, we refrained from analysing these categories. The results are expressed as adjusted HR (aHR) with 95% CI. Individuals with rheumatoid arthritis or axial spondyloarthritis were compared with counterparts matched on age, sex, month and year on the index record. Both incident and prevalent cases of mental disorders were considered.

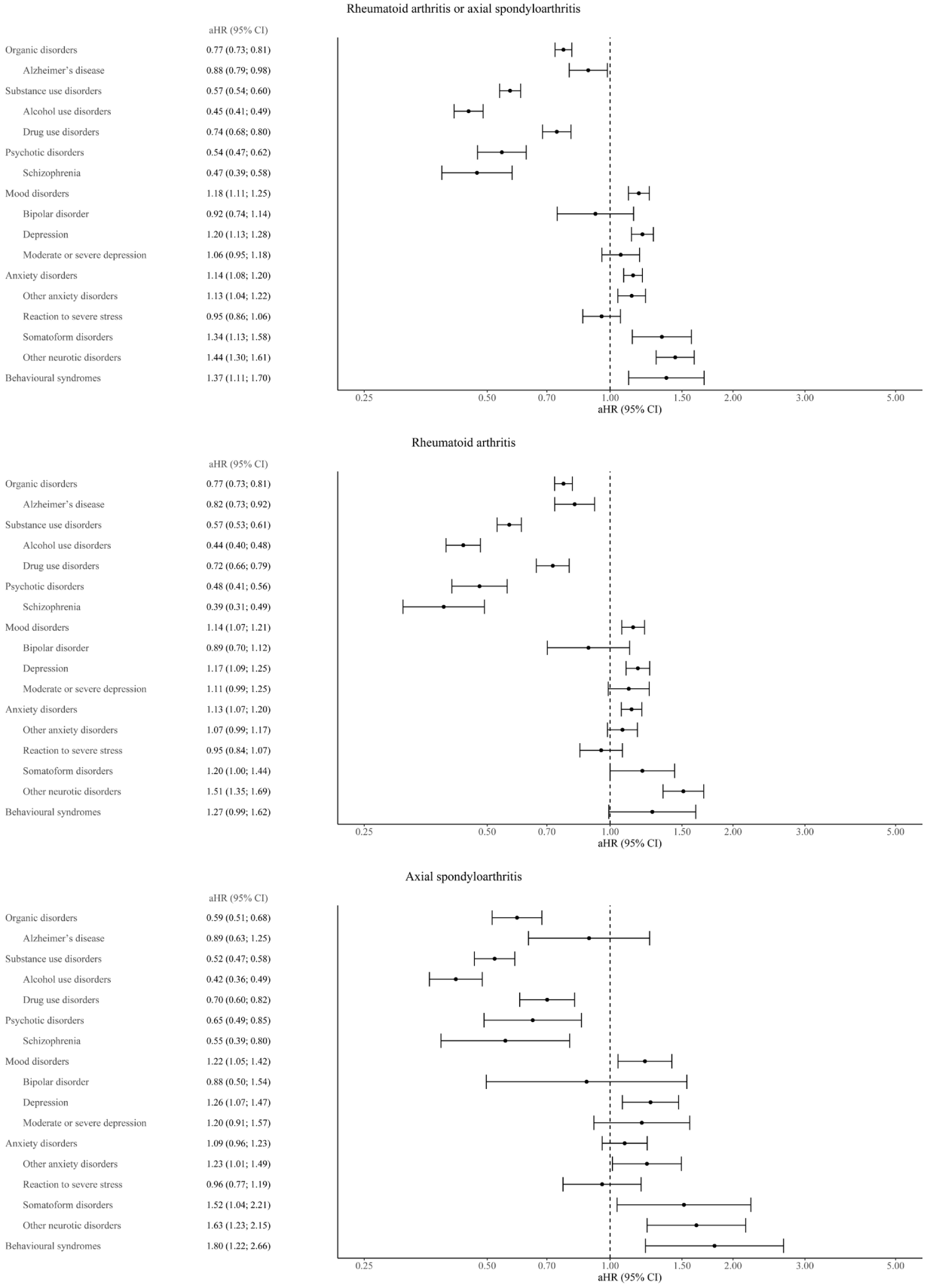

Figure 2 Associations between rheumatoid arthritis or axial spondyloarthritis and mental disorders compared with matched counterparts with other chronic illnesses. The results are expressed as adjusted HR (aHR) with 95% CI. Individuals with rheumatoid arthritis or axial spondyloarthritis without any 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 on the index record. We adjusted for the number of hospitalisations in the period of 5 years before the index record. Both incident and prevalent cases of mental disorders were considered.

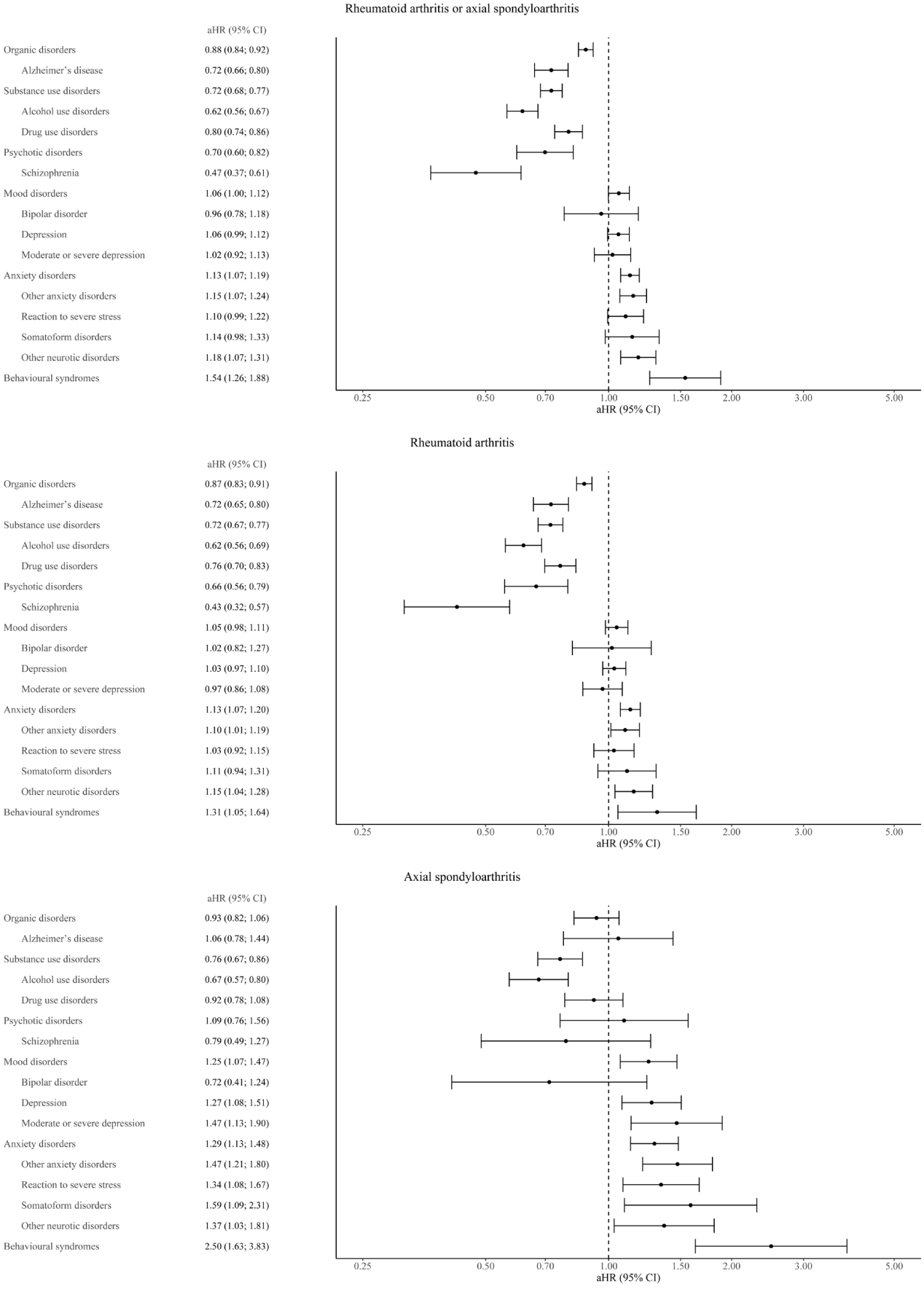

Figure 3 Associations between rheumatoid arthritis or axial spondyloarthritis and mental disorders, excluding people with pre-existing mental disorders. The results are expressed as adjusted HR (aHR) with 95% CI. Individuals with rheumatoid arthritis or axial spondyloarthritis were compared with counterparts matched on age, sex, month and year on the index record. Only incident cases of mental disorders were considered.

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 randomisation studies failed to detect any evidence of causality between RA and depression,[30 31] while another Mendelian randomisation 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 randomisation is highly sensitive to genetic instrument strength. While 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 randomisation findings do point to an alternative primary explanation for the presence of depression in people with RA.

RA onset earlier in life might translate into 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 medications 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 in international clinical guidelines for RA over the course of this study, while this medication is generally not indicated for treatment of axSpA. A small, early-phase trial of methotrexate indicated antidisease 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 under-reporting or underdiagnosis cannot be discounted, given that people with schizophrenia are well known for having reluctance or difficulties in accessing or engaging with healthcare 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 with 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 a consistent inverse association between RA and Alzheimer's disease. A similar inverse association was demonstrated by register-based studies from Taiwan[38] and the UK.[39] A Mendelian randomisation 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 demonstrated an elevated risk for Alzheimer's disease using register-based data from the UK.[40]

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

Methodological considerations

The strengths of this study include the use of 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 (ie, 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 (ie, 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 sociodemographic, 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 the 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 the associations between 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 recorded on the index record; however, this can differ from both the first-ever diagnosis age and the symptom onset age for a given individual.

Lastly, 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. The findings 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 the management of RA and axSpA contain no[43] or only perfunctory[44 45] mention of the importance of assessing and treating mental disorders in people with these inflammatory illnesses.

Thus, concerted efforts to better recognise 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.

Author affiliations
[1]Department of Psychiatry, University of Cambridge, Cambridge, UK
[2]Department of Public Mental Health, National Institute of Mental Health, Klecany, Czechia
[3]Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus, Denmark
[4]Department of Psychiatry, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czechia
[5]Clinical Center, National Institute of Mental Health, Klecany, Czechia
[6]Third Faculty of Medicine, Charles University, Prague, Czechia
[7]Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK
[8]Institute of Rheumatology, Prague, Czechia
[9]Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czechia
[10]Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[11]Department of Social Work, Faculty of Arts, Charles University, Prague, Czechia
[12]Institute of Clinical Sciences and MRC Laboratory of Medical Sciences, Imperial College London, London, UK

X Emanuele Felice Osimo @eosimo

Contributors 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 the results, performed the code review, and provided critical revisions to the manuscript. PM, MFL and PW contributed to designing the study and interpretation of the results and provided critical revisions to the manuscript. MO and KP contributed to designing the study and provided critical revisions to the manuscript. EFO contributed to designing the study, literature review and interpretation of the results, and wrote a substantial part of the manuscript. PBJ contributed to designing the study and interpretation of the results, and provided supervision and critical revisions to the manuscript. MH contributed to designing the study, literature review and interpretation of the results, and provided critical revisions to the manuscript. All authors approved the decision to submit for publication. TF and KM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. TF is the guarantor.

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ORCID iDs
Tomáš Formánek http://orcid.org/0000-0002-6740-6860
Emanuele Felice Osimo http://orcid.org/0000-0001-6239-5691
Peter B Jones http://orcid.org/0000-0002-0387-880X

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