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ORIGINAL ARTICLE

Depression as a risk factor for the development of rheumatoid arthritis: a population-based cohort study

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ABSTRACT

Objectives Major depressive disorder (MDD) is associated with increased levels of systemic proinflammatory cytokines, including tumour necrosis factor alpha. As these cytokines are pathogenic in autoimmune diseases such as rheumatoid arthritis (RA), our aim was to explore on a population-level whether MDD increases the risk of developing RA.

Methods A retrospective cohort study was conducted using The Health Improvement Network (THIN) database (from 1986 to 2012). Observation time was recorded for both the MDD and referent cohorts until patients developed RA or were censored. Cox proportional hazards models were used to determine the risk of developing RA among patients with MDD, accounting for age, sex, medical comorbidities, smoking, body mass index and antidepressant use.

Results A cohort of 403 932 patients with MDD and a referent cohort of 5 339 399 patients without MDD were identified in THIN. Cox proportional hazards models revealed a 31% increased risk of developing RA among those with MDD in an unadjusted model (HR=1.31, 95% CI 1.25 to 1.36, p<0.0001). When adjusting for all covariates, the risk remained significantly increased among those with MDD (HR=1.38, 95% CI 1.31 to 1.46, p<0.0001). Antidepressant use demonstrated a confounding effect that was protective on the association between MDD and RA.

Conclusion MDD increased the risk of developing RA by 38%, and antidepressants may decrease this risk in these patients. Future research is necessary to confirm the underlying mechanism of MDD on the pathogenesis of RA.

Key messages

What is already known about this subject?

- Recent evidence suggests major depressive disorder (MDD) may be associated with increased levels of systemic inflammatory cytokines that are thought to be important in the pathophysiology of rheumatoid arthritis (RA).

What does this study add?

- Based on the inflammatory hypothesis of depression, we investigated the possibility that MDD may increase the risk of developing RA.
- In this study evaluating over 5 million patients over 25 years, we found that patients with MDD were at a 38% increased risk of subsequently developing RA.
- Antidepressant medication use had a confounding effect that was protective on the association between MDD and RA.

How might this impact on clinical practice?

- MDD may be a risk factor for development of RA, but this risk may be lowered through treatment with antidepressants.

INTRODUCTION

The pathophysiology of rheumatoid arthritis (RA) is a consequence of local and systemic inflammation driving joint damage, morbidity and mortality.[1–3] However, the inciting risk factors for disease development remain less well understood. Some risk factors for RA have been demonstrated consistently, such as female sex, smoking and genetics (HLA-DR4),[1 4] but these only partially explain individual risk. At a molecular level, tumour necrosis factor alpha (TNFα), a proinflammatory cytokine, plays an important role in RA pathophysiology.[2 5] However, it remains unknown whether elevated TNFα levels induced by means of a different disease process could independently increase the risk of developing RA.

Patients with RA are recognised to have an increased risk of major depressive disorder (MDD),[6] and a systematic review and meta-analysis has shown that the prevalence of MDD in patients with RA is estimated to be 16.8% (95% CI 10% to 24%).[7] Interestingly, we previously demonstrated that MDD can increase the risk of developing psoriatic arthritis, another inflammatory arthropathy,[8] but it is not known whether MDD can increase

the risk of RA. MDD has been identified to have a direct effect on systemic inflammation.[9] For instance, individuals with MDD exhibit increased serum concentrations of TNFα relative to healthy controls independent of underlying inflammatory disease.[10] A relationship exists between serum TNFα concentrations and brain 5-HTT (serotonin) receptors, proposing a molecular link between MDD and inflammation.[11] Based on this and the association of TNFα with RA pathogenesis, it is possible that exposure to MDD may increase the risk of subsequently developing RA. In addition, MDD is known to be associated with numerous adverse health behaviours such as physical inactivity, poor dietary choices and smoking and these could be contributing factors towards an elevated RA risk.

Based on the understanding that MDD may have inflammatory associations and can predispose to adverse health behaviours, we hypothesised that patients with MDD are at a significantly increased risk of developing RA compared with the general population without MDD.

METHODS

Data source

THIN is an electronic database that contains general practice medical records from over 5% of the UK population, with over 25 years of follow-up.[12] In the UK, specialist referrals are sent from each patient's general practitioner (GP) and information from specialists' offices are returned to the GP and subsequently recorded in THIN. It has also been demonstrated that patients registered in THIN have similar age and sex distributions to the general UK population.[13 14] Therefore, THIN is well suited for epidemiological studies and has been used previously for the study of both RA[15] and MDD.[12]

Study population

We identified all individuals aged 10–90 years who have been registered in THIN for at least 1 year. Any individuals with a diagnostic Read code for RA or MDD during the first year of follow-up in THIN were excluded so that only incident cases of RA and MDD were considered. Among patients included in the study, their inception date in THIN was considered as the start of follow-up in the study.[16]

Exposure

The primary exposure in this study was incident MDD, defined by the presence of any diagnostic Read code for MDD, excluding patients with any codes for bipolar disorder, after at least 1 year in THIN, as done previously.[8 16] The date of exposure was identified by the first recorded MDD Read code. Cases of MDD developing after RA were excluded from this study in order to ensure the appropriate temporal association between MDD and incident RA.

Outcome

The primary outcome of interest was development of RA. A diagnosis of RA was defined by the presence of at least one diagnostic Read code for RA.[15] Eligible Read codes were determined by two physicians (CB, a rheumatologist and RTL, a physician-scientist with expertise in musculoskeletal health), in a similar fashion to previous research.[15] All patients were followed until the earlier of (1) first diagnostic RA Read code, (2) transfer out of practice, (3) death, (4) end of data collection period (up to 15 May 2012). Observations were censored in patients where a RA Read code was not recorded during the study period. As described above, we ensured only incident cases of RA were considered by excluding any patient with a Read code for RA within 1 year of registration in THIN.

Covariates

Covariates assessed included baseline age (assessed both continuously and categorically (onset age <45 or ≥45)),[17] sex, body mass index (BMI) (kg/m^2), smoking status (current, ex-smoker or never), other major medical comorbidities (defined using the Charlson Comorbidity Index) and use of antidepressants. The baseline values for age, sex, BMI and smoking status were all determined based on their value at the time point closest to each patient's start date in the study. Due to the large proportion of missing data for BMI, we performed multiple imputation (m=20) on the BMI variable. Charlson Comorbidity Index for each patient considered all Read codes up to 3 years from the patient's start date.[18] Antidepressant use was classified based on the presence of at least one antidepressant drug code during the study period and occurring after the MDD diagnosis in the exposed cohort. Antidepressant use included any agents from the following categories: (1) selective serotonin reuptake inhibitors, (2) selective norepinephrine reuptake inhibitors , (3) serotonin modulators, (4) atypical antidepressants, (5) monoamine oxidase inhibitors or (5) tricyclic antidepressants.

Statistical analysis

All analyses were performed using STATA/MP V.13.1 with a significance level set at alpha 0.05. The study index date was the patient's start date in THIN, the time of exposure was the date of first diagnosis of MDD (if applicable) and the time of outcome was the first date on which one of the outcome criteria were fulfilled. For patients who developed MDD, their data were partitioned and analysed according to unexposed time (before diagnosis) and exposed time (after their first MDD Read code). This was done to minimise the risk of survival bias.[19] Cox proportional hazards models were used to evaluate the risk of developing RA based on the exposure of MDD, expressed as a HR. An unadjusted model and a fully adjusted model were developed, with all covariates included in the full model. To identify any variables that produced a confounding effect, a backwards elimination

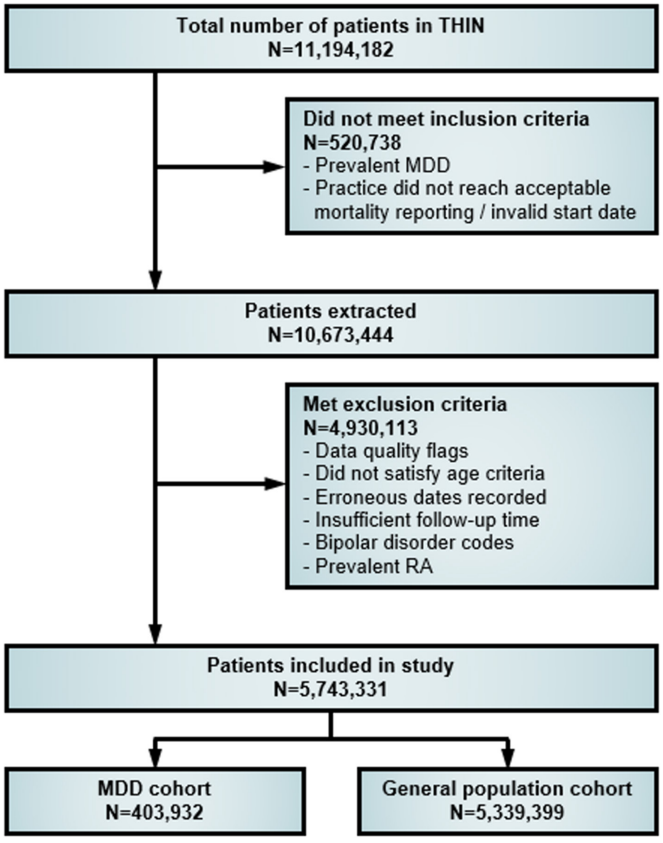

Figure 1 Study flow diagram showing selection of patients from THIN for inclusion in analysis. MDD, major depressive disorder; RA, rheumatoid arthritis.

procedure was used where each term was removed from the model, one at a time to determine whether they induced a substantial (>10%) change to the estimated HR. The proportional hazards assumption was evaluated by testing the Schoenfeld residuals and constructing a log-log plot, and based on these, it was concluded that there was no evidence of violation.

Sensitivity analyses were conducted to evaluate whether the association found was robust against modifications to the inclusion criteria. As such, we applied a 3-year washout period for MDD, where patients with a diagnosis of MDD during those periods were considered prevalent and therefore excluded from analyses. Additionally, a sensitivity analysis was used to establish sufficient follow-up time for outcomes to be observed by imposing a minimum 3 years of follow-up time in THIN. To explore the impact of imposing a minimum timeframe between the exposure and outcome, a sensitivity analysis was performed to restrict the results to patients with a minimum of 6 months between a diagnosis of MDD and RA. A more specific case definition of RA was tested in an additional sensitivity analysis where patients were only coded as having RA if they had any RA Read code and the presence of at least one disease-modifying antirheumatic drug (DMARD) medication. Last, since some patients in the general population were exposed to antidepressants without an MDD Read code (as these medications are often used for other non-MDD indications), a sensitivity analysis was performed where the risk of developing RA was compared between those in the general population who were exposed, to those who were not exposed to antidepressants. As well, the proportion of patients who developed RA among those who were exposed was compared with the patients unexposed to antidepressants in the MDD cohort. These results were reported in a descriptive manner to help determine whether there may be an independently protective effect or confounding effect of antidepressants on the risk of developing RA.

RESULTS

We identified a cohort of 403 932 patients with MDD and a referent cohort of 5 339 399 patients in the general population without an MDD diagnosis at any time during observation. A flow diagram of patient disposition is demonstrated in figure 1. Patients included in this study had similar age and sex distributions to the population before applying the exclusion criteria (table 1). The median follow-up time for patients included in the study was 6.7 years (IQR: 9.3 years). Overall, patients in the MDD cohort were older, more likely to be female, current smokers, more likely to have at least one comorbid disease and use antidepressants (all p<0.0001, table 1). In the MDD cohort, 88.3% of patients had used antidepressants at any point during follow-up compared with 15.1% of patients in the referent cohort. Among those with MDD, there were 2192 patients who developed RA (0.54%) with an incidence rate of 85.4 per 100 000 person-years. In the general population cohort, there were 24 021 patients who developed RA (0.45%) with an incidence rate of 52.8 per 100 000 person-years. Patients in the MDD cohort developed RA at an earlier age (median: 56.0, IQR: 19.6 years) compared with those in the referent cohort (median: 61.0, IQR: 21.9 years). Figure 2 demonstrates the Kaplan-Meier failure curves for the MDD and referent cohorts on the risk of developing RA.

The crude, unadjusted risk of developing RA was 31% higher among those with MDD compared with the general population (HR=1.31, 95% CI 1.25 to 1.36, p<0.0001) (table 2). Initially, evidence of effect modification by age was detected statistically (p<0.0001); however, when results were stratified by younger onset of MDD<45 years vs older onset≥45 years,[17] the estimated HRs differed by approximately 6%, thus to focus on clinical relevance, the age interaction was suppressed and a fully adjusted model was constructed. After adjusting for age (as a continuous variable), sex, smoking status, BMI, Charlson Comorbidity index and antidepressant use, the risk of developing RA among those with MDD remained significantly increased (HR=1.38, 95% CI 1.31 to 1.46, p<0.0001). In a backward elimination procedure used to examine whether any variables had a confounding effect, only the removal of the antidepressant variable produced a substantial change (ie, ≥10%) to the estimated HR. Antidepressants appeared to produce a confounding

Table 1 Baseline characteristics of patients with MDD and the general population

Variable	MDD cohort (n=403 932)	General population (n=5 339 399)	P values
Age			<0.0001
Median (IQR) years*	36.6 (24.0)	35.5 (27.7)	
Sex			<0.0001
Females†	40 749 (65.1%)	2 648 590 (49.6%)	
Obesity status			<0.0001
BMI<30 kg/m^2	156 437 (38.7%)	2 231 430 (41.8%)	
BMI≥30 kg/m^2	33 021 (8.2%)	369 156 (6.9%)	
Missing‡	214 474 (53.1%)	2 738 813 (51.3%)	
Smoking status			<0.0001
Current	105 256 (26.1%)	1 004 206 (18.8%)	
Ex-smoker	32 481 (8.0%)	474 452 (8.9%)	
Never	187 864 (46.5%)	2 711 850 (50.8%)	
Missing	78 331 (19.4%)	1 148 891 (21.5%)	
Charlson comorbidity index§			<0.0001
0	314 913 (78.0%)	4 339 935 (81.3%)	
1	64 856 (16.1%)	637 332 (11.9%)	
2	11 864 (2.9%)	139 174 (2.6%)	
3	4270 (1.1%)	52 177 (1.0%)	
≥4	8029 (2.0%)	170 781 (3.2%)	
Antidepressant use			<0.0001
Users	356 493 (88.3%)	804 444 (15.1%)	
Non-users	47 439 (11.7%)	4 534 955 (84.9%)	

Values show the number (per cent) of patients with a given characteristic.
*Median age in all patients before exclusion—MDD: 36.5 (23.8); General population: 35.1 (29.0).
†Sex (%) in all patients before exclusion—MDD: 65.3% females; General population: 51.4% females.
‡BMI—represented here as baseline data before multiple imputation.
§Higher=more severe or greater number of medical comorbidities.
BMI, body mass index; MDD, major depressive disorder.

association which had a protective effect on the risk of developing RA.

In a sensitivity analysis where the initial washout period was extended from patients being registered in THIN for a minimum of 1 year to 3 years, the risk of RA among those with MDD remained significantly elevated (HR=1.40, 95% CI 1.28 to 1.53, p<0.0001). Similarly, a sensitivity analysis used to ensure a minimum of a 3year follow-up period in THIN also demonstrated that the hazard remained significantly higher in those with MDD (HR=1.34, 95% CI 1.24 to 1.45, p<0.0001). When a minimum of 6 months between a diagnosis of MDD and RA was applied, a similar significant association was observed (HR=1.28, 95% CI 1.18 to 1.38, p<0.0001). Using a more specific definition of the RA outcome where a patient had to have a Read code and a code for a DMARD medication, the results remained significant (p<0.0001) but increased in magnitude (HR=1.63, 95% CI 1.54 to 1.72, p<0.0001). Last, when assessing the effect of antidepressants on RA risk among the general population without an MDD code, it was found that 0.68% of those using antidepressants developed RA compared with 0.41% among those who did not use antidepressants. In the cohort with MDD, the risk was lower among those using antidepressants where 0.51% developed RA compared with 0.77% among those not being treated with antidepressants.

DISCUSSION

The present study highlights that patients with MDD are at a 38% increased risk of subsequently developing RA. In perspective, this risk is about equivalent or slightly higher than the risk imposed by obesity on development of RA.[20] This increased risk was not sensitive to the washout period, follow-up or exposure time in this study, but antidepressant medication was identified as a confounder resulting in the risk of RA being reduced, underscoring the important effect of MDD on developing RA. This finding adds to our understanding on the relationship between MDD and inflammatory arthritis, where previous research has shown MDD increases the

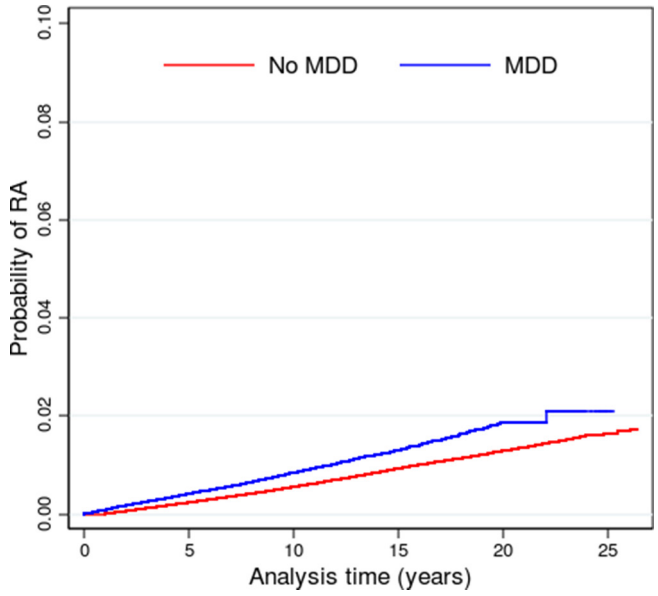

Figure 2 Kaplan-Meier failure curves with development of RA stratified by depression exposure. Here, it can be seen that study follow-up was up to 25 years and that the probability of developing RA was greater among those with MDD (blue) compared with the general population cohort group (red). MDD, major depressive disorder; RA, rheumatoid arthritis.

risk of psoriatic arthritis.[8] Moreover, these results provide evidence that a bidirectional relationship between MDD and RA may exist, as it has previously been well established that patients with RA experience an increased risk of MDD.[6]

Table 2 HRs for the risk of RA

Model	HR (95% CI)	P values
Unadjusted model		
Depression	1.31 (1.25 to 1.36)	<0.0001
Multivariable adjusted model*		
Depression	1.38 (1.31 to 1.46)	<0.0001
Age (per 1 year)	1.03 (1.03 to 1.03)	<0.0001
Male sex	0.48 (0.46 to 0.49)	<0.0001
Charlson comorbidity index	1.41 (1.39 to 1.43)	<0.0001
BMI	1.02 (1.02 to 1.03)	<0.0001
Smoking		
Current	1.74 (1.69 to 1.80)	<0.0001
Ex-smoker	1.40 (1.34 to 1.46)	<0.0001
Antidepressant use	0.74 (0.71 to 0.76)	<0.0001

Cox proportional hazards models were used to estimate the HRs of developing RA based on whether patients had depression or not (ie, depression vs general population). Depression significantly increases the risk of developing RA when using unadjusted models as well as models accounting for numerous covariates. Values show the number (per cent) of patients with a given characteristic.
*Observations with missing data were omitted from the models, except BMI which was handled using multiple imputation.
BMI, body mass index; RA, rheumatoid arthritis.

Importantly, while the risk of RA was higher among those with MDD, the absolute risk of RA remained low. Thus, clinically, our data would not support any role for RA screening among those with MDD; however, physicians involved in the care of patients with MDD should be aware that RA may be relatively more common among this group, and so prompt referral to a rheumatologist should be initiated if clinical suspicion for RA arises.

MDD is known to be associated with detrimental health behaviours such as poor diet and physical inactivity.[21] It remains possible that these maladaptive health behaviours, indirectly captured in our study as MDD, contribute to an increased risk of RA. Supporting this possibility, it has been shown that RA flares can be exacerbated by diet[22] and that regular physical activity can help improve function.[23] Alternatively, recent studies in molecular neuropsychiatry have demonstrated that MDD is associated with increased levels of serum TNFα[10] and increased TNFα levels in patients with MDD is correlated with increased serotonin transporter availability,[11] together suggesting a systemic inflammatory component in MDD. RA severity is known to be associated with elevations in TNFα levels,[24] and thus it remains possible that MDD drives a state of inflammation leading to an increased risk of RA in predisposed individuals. Unfortunately, as THIN does not routinely document diet, physical activity or inflammatory markers, it is presently not possible to conclude which of the above possible mechanisms contributes to the observed increased risk of RA among those with MDD. However, our identification of an association between MDD and RA provides impetus for future studies to test the influence of diet, physical activity and inflammation on driving RA development. Of note, a recent study from the USA documented the risk of RA increased in a dose-response relationship with the number of post-traumatic stress disorder (PTSD) symptoms a patient experienced.[25] PTSD is a psychiatric disorder also associated with both systemic inflammation[26] and poor health behaviours,[27] thus it seems our findings are consistent with this previous work.

Our study also revealed that patients with MDD treated with antidepressants were at a lower risk of RA (0.51%) compared with patients with MDD without antidepressant medication (0.77%). These results represent the possibility that treated MDD has a reduced risk of RA compared with untreated MDD. Treated MDD may improve health behaviours or mitigate any inflammatory associations and render these patients more similar to the general population without MDD. When exploring the relationship between antidepressants and RA development in the general population, the risk was higher among those using antidepressants (0.68%) compared with those not using these medications (0.41%), thus suggesting that antidepressants are not likely to have an independently protective effect

on RA pathogenesis. It is possible that these patients without MDD are being treated with antidepressants for other health problems, which may slightly increase their risk of developing RA. As such, it appears that treating depression with antidepressants can help to lower the risk of developing RA but there is insufficient evidence to suggest any role for the prevention of RA in general by using antidepressants. One limitation in this conclusion is that those patients with MDD pursuing/benefiting from non-pharmacological therapeutic strategies including psychotherapy are not identifiable in our dataset.

This analysis capitalises on a large sample size with long follow-up, which allowed us to study the relatively infrequent outcome of RA on a population-level. However, it is also important to recognise that while numerous covariates were considered, there may be additional variables not accounted for in this study (eg, antibodies), and we are unable to develop a causal model for why MDD increases the risk of RA. Additionally, given the large sample size and high statistical power of this study, it is important to prioritise the clinical relevance of any statistically significant results. Although we excluded a large number of patients from THIN by applying a stringent exclusion criteria (to enable survival analyses on patients with complete time to event data), the risk of selection bias is low given that the age and sex distribution in the included referent cohort resembled the general population closely and is consistent with existing literature.[28] While misclassification of cases is always a risk in database research, this would be expected to occur at random which would dilute the overall HR observed towards the null value and thus provide a conservative estimate of risk. Last, although our focus in this study was not to investigate treatment response directly, THIN is a suboptimal data source for studying treatment response or length of treatment since it does not have sufficiently detailed data to make inferences about adherence, severity or the time point at which remission or relapse of MDD may have occurred. As such, future studies should aim to further investigate the role of antidepressant treatment for MDD in the prevention of chronic autoimmune diseases like RA.

In conclusion, this study has demonstrated that patients with MDD have approximately a 38% increased risk of developing RA, and this risk seemed to be reduced when patients with MDD were treated with antidepressants.. While the precise mechanism by which MDD contributes to this increased risk remains unknown, future research should investigate the possibility of adverse health behaviours and systemic inflammation as inciting factors. Clinically, prompt referral to rheumatology should be made when patients with MDD present with musculoskeletal symptoms characteristic of RA.

Contributors IAV, RTL and CB developed the study topic. CB contributed expert advice on RA. SBP and AGMB provided expert advice on MDD. IAV, ADF and MWL contributed to data systems development and extraction. GGK, MGS, AGMB, SBP and CB provided methodological expertise. Statistical analyses were performed by IAV with critical review by RTL, ADF, MWL, GGK, SBP and CB. IAV drafted the manuscript, tables and figures, with all authors providing critical review. All authors approved the final version of this manuscript.

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Competing interests None declared.

Patient consent Not required.

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