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Common mental disorders within chronic inflammatory disorders. A primary care database prospective investigation

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Objectives: There is inconsistent evidence about the association between inflammatory disorders with depression and anxiety onset in a primary care context. The study aimed evaluate the risk of depression and anxiety within multisystem and organ-specific inflammatory disorders.

Methods: Prospective cohort study with primary care patients from the UK Clinical Practice Research Datalink diagnosed with an inflammatory disorder between 1st of January 2001 and 31st of December 2016. These patients were matched on age, gender, practice, and index date with patients without an inflammatory disorder. The study exposures were seven chronic inflammatory disorders. Clinical diagnosis of depression and anxiety represented the outcome measures of interest.

Results: Among 538,707 participants, the incidence of depression ranged from 14 per 1000 person-years (severe psoriasis) to 9 per 1000 person-years (systemic vasculitis), substantively higher compared to their comparison group (5 to 7 per 1000 person-years). Hazard ratios (HR) of multiple depression and anxiety events were 16% higher within inflammatory disorders (HR, 1.16, 95%CI 1.12-1.21, p<0.001) compared to the matched comparison group. The incidence of depression and anxiety was strongly associated with the age at inflammatory disorder onset. The overall HR estimate for depression was 1.90 (95%CI, 1.66-2.17, p<0.001) within early onset disorder (<40 years of age) and 0.93 (95%CI, 0.90-1.09, p=0.80) within late-onset of disorder (≥60 years of age).

Conclusions: Primary care patients with inflammatory disorders have elevated rates of depression and anxiety incidence, particularly those patients with early onset inflammatory disorders. This finding may reflect the impact of the underlying disease on patients' quality of life, although the precise mechanisms requires further investigation.

Keywords: Autoimmune diseases, Epidemiology, Inflammation, Mental Health, Primary care

Key messages

What is already known on this subject?

- Several cross-sectional studies suggested but did not establish a contributory role of inflammation in the initiation of depression and anxiety within patients diagnosed with chronic inflammatory disorders.

What does this study add?

- In a prospective cohort study with 538,707 patients from primary care, a significant increment in the onset of new of depression and anxiety events was documented within organ-specific and multisystemic inflammatory disorders.
- The incidence of depression or anxiety varied with the age at inflammatory disorder onset.

How might this impact on clinical practice or future developments?

- The elevated risk of depression and anxiety means clinicians should be vigilant for early symptoms of depressive or anxiety in this highly at-risk group of patients.
- The risk was greater among patients with younger age at inflammatory disorder onset, supporting tailored preventative approaches early in the course of a chronic disorder.
- The study, however, does not demonstrate a causal relationship between inflammation with depression and anxiety.

Introduction

A growing body of evidence indicated that low-grade inflammation may play an influential role in the onset of depression and anxiety.[1] Past research has linked upregulated pro-inflammatory cytokines and increased levels of acute-phase reactants with changes in neurotransmitter and neuroendocrine functioning related to psychiatric disorders.[2 3] This evidence supports a link between depression and anxiety with inflammatory disorders (e.g. rheumatoid arthritis (RA), psoriasis, ankylosing spondylitis (AS)), and cross-sectional studies are in line with this suggestion. [4-7] Evidence from prospective studies exploring the role of inflammatory disorders in depression and anxiety onset were, however, inconsistent.[8 9] Little is known about the incidence of depression or anxiety across clinically diverse inflammatory disorders. Differences in genetic influences and treatment choices across inflammatory disorders may lead to variation in depression or anxiety onset.[10 11] The genetic association with human leukocyte antigen (HLA) alleles, for instance, was stronger within AS compared to RA.[10] Quantifying the extent to which the link between inflammatory disorders with depression vary by individual disorders may suggest mechanisms underlying specific relationships and ultimately facilitate targeted preventative approaches. There is substantive variation in the age of onset across individual inflammatory disorders that may also lead to differential association with depression or anxiety,[12 13] in turn more prevalent in early adult years. The incidence of depression or anxiety, thus, may be lower across disorders with late age at onset (e.g. RA) than those with early age at onset (e.g. Crohn's disease). The detection of disparities in mental health burden could guide treatment choice and effective tailoring of healthcare resources. The aim of the present study was to implement a prospective cohort study within a large primary care database to test the hypothesis that the incidences of depression or anxiety varied across specific inflammatory disorders. It was also hypothesised that depression or anxiety risk was greatest within people with an early age at disorder onset.

Methods

Data

A prospective matched cohort study design was implemented in the Clinical Practice Research Datalink (CPRD), among the world largest electronic medical records database. CPRD collects routine primary care data on over 14 million patients (≈6.7 million active) from around 675 practices throughout the UK National Health Service (NHS). All patients in the NHS are registered with a general practice that provides all their primary care and coordinates secondary and community care. Important diagnostic and therapy information from referrals to secondary or community care services are captured by primary care records. Patients included in the CPRD are broadly representative of the UK's wider population in terms of age, gender, and ethnicity.[14] The validity and accuracy of CPRD diagnostic and prescription data have been demonstrated across a wide range of disorders including cancer,[15] stroke,[16] COPD,[17] depression and anxiety,[18] rheumatoid arthritis,[19] inflammatory bowel disorders,[20] and autoimmune disorders.[21 22]

Study population

A cohort of primary care patients aged >18 years with a first-ever diagnosis of a chronic inflammatory disorder (psoriasis, Crohn's disease (CD) and ulcerative colitis (UC), RA, SLE, ankylosing spondylitis (AS), and systemic vasculitis (SV)) recorded between 1st of January 2001 and 30th of September 2016, who were depression or anxiety disorders free at the time of inflammatory disorder diagnosis were sampled from the CPRD. The date of diagnosis was defined as the index date. The index date for patients transferring into the practice was their practice registration date and the practice up-to-standard (UTS) date was used if a practice joined the data base during the recruitment period. The end of recruitment was the earliest of 30th of September 2016 or the death date or transferred out of the practice date. Patients

below the age of 18 at the time of diagnosis were excluded from the study sample because the presentation and course of inflammatory disorders might be different in younger people.[23] All diagnoses were derived from the medical codes recorded by family physicians in patients' electronic health records. These patients were matched (a 1:2 ratio of inflammatory exposed to 2 matched non-exposed) on age (year of birth), gender, practice, and index date with a group of patients without a chronic inflammatory disorder selected for this study during the recruitment period. Matched controls were assigned the index date of the inflammatory disorder diagnosis of the matched case. Similar to the inflammatory patients, matched controls with a diagnosis of depression or anxiety before the assigned index date were excluded from the analyses. Psoriasis patients are commonly classified into severe if they were prescribed a systemic therapy (i.e. methotrexate, azathioprine, cyclosporine, hydroxyurea) or phototherapy (psoralen and ultraviolet A) during the study period, or into mild psoriasis if no such treatment was recorded.[24 25] This classification has been validated with similar databases[26-28] and has also been used in this study. Data were extracted from the CPRD in September 2017.

Outcome

The study primary outcome measures were a new Read medical code for a diagnosis of depression or anxiety used as binary variables (yes/no).[29] The date of the first outcome code following an inflammatory disorder diagnosis was referred to as the outcome index date. Depression was broadly defined to include single episode of depression, recurrent depression events, and bipolar depressive events to allow for the possibility that chronic inflammation is implicated across the wider spectrum of the depressive disorder. In keeping with other studies,[30] anxiety was broadly defined to include generalised anxiety disorders, phobias, panic attacks, and panic disorders.

Covariates

Factors known to be associated with chronic inflammation and depression or anxiety were adjusted for in the analyses. These covariates included age (continuous), gender (male vs female), body mass index (<18.5, 18.5 to 25, >25 to <30, 30 to <35, and ≥35 kg/m^2), index of multiple deprivation (quintiles) , blood pressure (BP) (<120 mmHG, normal; 120-139 mmHg, borderline; ≥140 mmHg, hypertension), smoking (ex- or current vs never), drinking (ex- or current vs never), physical comorbidities (yes/no) (i.e. cancer, diabetes, stroke, coronary heart disease (CHD), dementia, epilepsy, chronic obstructive pulmonary disease (COPD), liver disorders, kidney disorders, insomnia), stressful life events (e.g. stress at home or at work), together with prescription of statins, antihypertensive, anti-diabetic, and hypnotics. Previous studies[31 32] linked corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) with increased risk of depression and were therefore also included as covariates. For each potential confounder the value closer to the index date and within the five years period prior to a chronic inflammation diagnosis was included. For instance, if a patient had two BP measures within 5 years prior to the baseline (e.g. at 4 years and at 2 years prior to baseline), the value closer to the study baseline (e.g. at 2 years) was included in the analyses. Expanding the baseline period to available data was found to enhance covariate sensitivity by capturing data that would otherwise be missed.[33]

Statistical analysis

The analyses were conducted in a time-to-event framework. Failure was classed as a new diagnosis of depression or anxiety. Participants contributed person-time to the analysis from the study start date (the later of the start of the participant's record in CPRD or the diagnosis date for a chronic inflammatory condition). Follow-up ended at the earliest of the study outcome date, the end of a participant's registration, the last date of CPRD data collection, or

date of death. All participants had at least 12 months of follow-up recorded had at least one medical event recorded from the study start date to the study end date.

A Cox proportional-hazards model for clustered data based on the matched pairs was implemented with the use of a multiple-failure events to allow for the possibility that each patient may experience more than one outcome event.[34] This approach permits analysis of data for each of multiple outcomes in a single model, allowing the most efficient use of each patient's data and reducing problems of multiple testing.[24] The multiple-failure model avoids the need to censor records at earlier outcome events or to test hypotheses separately for each outcome. Robust variance estimator was used to adjust for the dependency introduced by the matching variables. This approach is considered[35] superior to matched stratification as it allows for unbiased estimation of hazard ratios. Because confounding by matching variables cannot be excluded,[36] the estimation models adjusted for: matching variables (age, gender, practice, index year) and all study covariates listed above. A similar estimation was performed to estimate whether depression or anxiety onset varied with the age (<40, 40-49, 50-59, and 60 or over) at inflammatory disorder diagnosis. Additional analyses estimated the specific associations between each inflammatory condition with depression and anxiety in separate Cox regression models with robust estimate variance. The analyses used the Efron method to handle tied events. Forest plots were used to present measures of association for age subgroups and individual inflammatory disorder. A random-effects meta-analysis was implemented to evaluate heterogeneity by chronic inflammatory disorder and overall.[37] The proportionality assumption was tested and confirmed using Schoenfeld residuals. As this was an exploratory study no adjustment for multiple comparisons was made, and therefore marginally significant results may be type I errors. Several sensitivity analyses were conducted. Firstly, alternative follow-up times were used by starting the follow-up immediately after the inflammatory disorder diagnosis. Secondly, depression and anxiety

were redefined to include both a clinical diagnosis code plus a relevant prescription (i.e. antidepressant or anxiolytic drugs, respectively). Thirdly, stratification by matched pairs was implemented to account for the matching. Fourthly, to test the robustness of psoriasis findings, data on systemic therapy were used to classify RA and systemic vasculitis patients (the only sufficiently powered disorders) into mild (no systemic therapy) and severe (systemic therapy). The effect of competing risk on mortality was also assessed. Multiple imputation by chained equation was used to handle missing data. The analyses were implemented using Stata version 15.

Results

The analyses included 180163 patients with chronic inflammatory disorders (see Table 1) that were individually matched for age, gender, practice, and index date with 358544 control patients without a diagnosis of chronic inflammation. The median duration of follow-up was around 4 years for patients and controls. While clinical diagnosis and therapy data were comprehensive, among lifestyle factors missing information ranged from around 6% for smoking to 22% for alcohol status. Selective baseline characteristics of study participants are described in Table 1 (See Table S1 in Supplementary material for full data description).

Insert Table 1 about here

Figure 1 shows the across all inflammatory disorders, the incidence of both depression or anxiety was greater within cases compared to the matched controls. The highest incidence rate was observed within severe psoriasis (14 per 1000 person-years), followed by those diagnosed with CD and AS (12 per 1000 person-years). Similar trends emerged with regards to the incidence of anxiety (Figure S1 in the Supplement).

Insert Figure 1 about here

Table 2 presents the results of the analyses by study outcomes indicating increased hazard rates of depression and anxiety across all chronic inflammatory disorders. The strongest association was observed for severe psoriasis, being associated with a 71% increased rate of new depression onset (hazard ratio (HR) 1.71; 95% confidence interval (CI), 1.52-1.93, p-value<0.0001) compared to the matched comparisons. Regarding new anxiety onset, patients diagnosed with AS presented with the largest hazard rates (1.36, 1.23-1.51, p<0.0001) compared to their matched comparison group. Age-related analyses revealed higher depression and anxiety incidence among persons with early inflammatory disorder onset. Kaplan-Meier survival curves are presented in Figure S2, Supplementary material.

Insert Table 2 about here

Figure 2 displays the results from the multiple outcome models, with patients being allowed to experience either depression or anxiety in a random order. Compared to the matched group, patients with an inflammatory disorder experienced a 16% (1.16, 1.12-1.21, p<0.001) increased risk of depression or anxiety events. Patients diagnosed with CD presented with the highest hazard ratio (1.23, 1.13-1.33, p<0.001), while those with mild psoriasis with the lowest hazard ratio (1.08, 1.03-1.13, p<0.001). Age-based analyses (Figure 3) indicated that the pooled hazard rate for multiple depression or anxiety incidence was 1.71(1.59-1.84, p<0.001) among patients with early inflammatory disorder onset (<40 years of age), which declined to 0.93 (0.85-1.01, p=0.080) among those with late disorder onset (≥60 years) (See Figure S3 in the Supplement for findings among 40 to 49 and 50 to 59 years of age groups).

Insert Figure 2 about here

Insert Figure 3 about here

Sensitivity analyses

Sensitivity analyses using a more stringent criteria for depression and anxiety definition (e.g. clinical diagnosis plus corresponding drug prescriptions) resulted in modestly higher estimates, validating the robustness of the main findings (Figure S4 and Table S1). Analyses stratified by matched pairs endorsed the estimates and associations of the study findings. Systemic therapy-based sensitivity analyses indicated that both severe RA (1.43,1.28-1.59, $p<0.001$) and systemic vasculitis (1.65,1.20-2.25, $p<0.001$) presented greater risk of depression incidence relative to mild RA (1.36, 1.25-1.49, $p<0.01$) or mild systemic vasculitis (1.42,1.27-1.60, $p<0.001$).

Discussion

The main aim of the present study was to provide a comprehensive understanding about the burden of common mental disorders across specific inflammatory disorders within a primary care context. Within a large prospective design, several clinically diverse inflammatory disorders presented with a consistently elevated risk of depression and anxiety incidence. In particular, a 16% overall increased risk of multiple depression and anxiety events emerged across seven specific chronic inflammatory disorders (RA, psoriasis, CD, UC, SLE, SV, and AS). Associations were observed between incident depression with each specific inflammatory disorder, although the effect size was of lower magnitude than suggested by findings based on secondary care-based populations.[4] The reason for this discrepancy may be that a smaller proportion of patients with inflammatory disorders, those with most severe or active disease, are seen in secondary care.[38] In our study, the incidence of depression and

anxiety was higher for patients with severe psoriasis relative to those with mild psoriasis. This suggestion was substantiated in sensitivity analyses among RA and systemic vasculitis disorders.

The pooled incidence of depression and anxiety was considerably increased (71% increment) among primary care patients with early onset inflammatory disorder (<40 years of age) and less so (-7%) among those with late disorder onset (≥60 years of age). Early onset inflammatory disorders are associated with more widespread inflammation, increased frequency of active disease, and more aggressive disease manifestation and treatment compared to late-onset disorder.[39] Whether the increased incidence of depression or anxiety within early disorder onset was caused by increased disease activity or delay in disorder diagnosis and treatment (or their combined effect), needs further exploration.

All seven chronic disorders analysed in this study are connected by common underlying inflammatory mechanism and the consistently elevated rates of depression and anxiety incidence across them might support a potential role of inflammation in the pathogenesis of these disorders, though this suggestion was not directly tested in this study. The main alternative hypothesis that cannot be excluded from this study design is that depression and anxiety may represent emotional responses to the experience of living with a distressing and often debilitating inflammatory disorder. The psychosocial and physical effects of the inflammatory disorder might therefore contribute to the onset of depressive and anxiety symptoms. For example, increased depression and anxiety incidence among primary care patients with early disorder onset, as found in this study, may reflect these patients presenting with more extensive and severe manifestations of the inflammatory disorder.[40] The elevated rates of depression events among patients with severe psoriasis relative to those with mild

psoriasis seem to be in line with a disease response hypothesis. Pain, disfigurement, loneliness, and stigma associated with severe inflammatory disease indicators (e.g. eruptive psoriasis, multiple nail lesions), for example, could worsen patients' sleep quality and prevent them from full social participation, leading to the onset of depressive symptoms.[41]

The results of the present study raise important questions about the assessment and management of common mental health disorders among younger patients diagnosed with specific inflammatory disorders. Irrespective of whether psychological problems are the consequence of the emotional reaction to disease and disability or of a common inflammatory etiology, there seems a clear association between inflammatory disorders and depression or anxiety, especially for younger early-onset patients. Routine assessments of patients' mental health could lead to improved prevention and treatment outcomes. If further research supports the common inflammatory etiology hypothesis, then clinical intervention might target the inflammatory response itself. Renewed interest in the potential effectiveness of immunomodulatory therapies (e.g. new biologics, methotrexate) for the prevention of treatment-resistant depression may indicate one way forward.

Previous prospective studies explored the association between depression and anxiety with specific inflammatory disorders. [9 42] Marrie et al.,[9 43] for example, documented somewhat higher incidence rates of depression and anxiety among patients with RA and IBD. Marie et al.' studies did not adjust for differences in chronic illnesses (e.g. CVD, diabetes, CKD) at baseline, did not account for matching in their analyses, used a different case definition (e.g. exclusion of cases within a 5-year period from index date), and relied on a more local population. These variations may account for the observed differences in effect size between our and Marrie et al. findings. Meesters et al.[44] also documented higher incidence rates of

depression events among AS patients from primary care compared to our findings, possibly due to previous study failure to adjust for other covariates apart from age and gender. An earlier study found no increased risk of depression among patients diagnosed with CD or ulcerative colitis[42]: this may reflect previous study' lack of a comparison group or shorter follow-up (<5 years). Recent studies[6 27] indicated greater incidence of depression among patients diagnosed with severe psoriasis relative to those with mild psoriasis, as observed in this study. The decline in depression incidence with age at disorder onset is in line with an earlier systematic review among RA patients,[4] and extends previous findings to anxiety.

Strengths and limitations

The present study has several strengths including nationally representative primary care population, prospective study design, and clinically valid diagnoses of inflammatory disorders, depression and anxiety. The inclusion of primary care patients with systemic and organ-specific inflammatory disorders, ensures the generalisability of the study findings to real-world clinical practice. While our data possibly contains all diagnoses issued within primary care, it may be less complete with regards to diagnoses made in secondary or community care.[45] Nine out of ten adults with mental health disorders are supported in primary care in the UK, implying that only a small number of cases are not captured by the CPRD. The use of antidepressant and anxiolytics therapies as sensitivity analyses may have also mitigated against diagnostic bias, given that drug prescribing is often considered a reliable marker for case identification.[46] Clinicians may be more alert (or ask different questions) to depressive or anxiety symptoms among patients with inflammatory disorders due to increased contact with the healthcare system, and thus more likely to identify relevant cases. The mean number of primary care consultations, however, was similar between inflammatory patients and matched controls (data not shown). The precise timings of the

onset of exposure or outcome measures cannot be determined precisely in observational data, precluding robust causal inferences. To mitigate against this concern, the analyses excluded outcome measures that occurred during the first 12 months following an inflammatory disorder diagnosis. Our large study sample comprised a heterogeneous group of patients with distinctive underlying disease severity and symptomatology, potentially masking subgroups of patients that could present with clinically significant mental disorders. This suggestion is supported by our finding with regards to severe psoriasis and age at inflammatory disorder diagnosis. A method of analysis that did not allow for matching might give slightly wider CIs and larger p values than a matched analysis.[47] Sensitivity analyses that adjusting for matching validated the study main findings. We cannot exclude the possibility that the comparison group included patients diagnosed with other less common inflammatory disorders (e.g. bullous skin diseases, Sjogren syndrome). This concern may have attenuated the true risk of depression or anxiety within chronic inflammatory disorders. The study primary aim was to model initial inflammatory disorder status (e.g. psoriasis, RA, SLE) and therapy (e.g. NSAIDs, corticosteroids), along with patients' socio-demographic and clinical data to patients' overall risk for future depression or anxiety onset. The analyses, however, did not model potential post-diagnosis mediators and moderators for depression or anxiety onset, including temporary changes in underlying disease severity, treatment choices, and inflammatory responses. These are clinically relevant questions that deserve detailed investigation with future prospective studies. The study only differentiated between mild and severe psoriasis. The smaller sample of patients within the rest of inflammatory disorders precluded a similar classification. This concern also applied to patients with psoriatic arthritis that were classified as psoriasis. Given that the definition of severe of psoriasis was based on DMARD exposure, however, it is possible that patients with psoriatic arthritis were included in the severe psoriasis subgroup. Sensitivity analyses within RA and systemic vasculitis

disorders endorsed psoriasis severity results increasing confidence in the robustness of the study findings. Future studies with larger IBD, SLE, and AS samples are also required to confirm the link between inflammatory disorder severity with study outcomes. Missing data on lifestyle covariates can compromise the results of statistical analysis but use of multiple imputation and appropriate sensitivity analyses should have mitigated some of this risk. A larger proportion of women were diagnosed with AS in this study, which is contrary to other studies showing higher AS rates among men.[48]The study findings about the incidence of depression or anxiety may, thus, not be generalisable to the wider AS population. This concern was likely caused by the matching of patients and controls on gender, leading to intentional non-representativeness. In analytical studies where the aim is to explore exposure-outcome association (as in this study), however, population representativeness is not considered necessary or desirable.[49] Richiardi et al.,[50] for instance, suggested that non-representativeness increases the power to assess main effects and effect modification, and that valid statistical inferences can be made when adjusting for confounders. Primary care patients diagnosed with an inflammatory disorder were at greater risk of new depression and anxiety onset compared to matched patients without an inflammatory disorder, a risk that was particularly elevated among patients with early onset of chronic inflammatory disorder. These findings may reflect either a response to the physical effects of living with a chronic inflammatory disorder, or a role for inflammation in the genesis of depression and anxiety. The latter hypothesis deserves further attention as it may offer the opportunity for new therapeutic approaches to anxiety and depression, but first the question of whether depression is a consequence of inflammation or is a reaction to experiencing a chronic illness deserves further exploration. Studies evaluating modifiable mediators for depression and anxiety incidence across specific inflammatory disorders are also warranted.

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The study was approved by the Independent Scientific Advisory Committee (reference No. 17_036RA).

Contributors AD, MF, AB, KD, CP, DA, RS, SH, and MH were responsible for study design. AD was responsible for data acquisition. AD analysed the data and wrote the manuscript. All authors critically revised the manuscript and approved the final version.

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Table 1*. Participants' characteristics at baseline assessment. Figures are numbers and percentages unless otherwise specified.

	RA	**Psoriasis**		**CD**	**UC**	**SLE**	**Vasculitis**	**AS**	**Total**	
		Mild	Severe						Exposed	Unexposed
N	37399	84184	6528	10453	23291	3604	14177	10363	180163	358544
Follow-up±	4(2,8)	5(2,8)	6(3,9)	4(2,8)	4(2,8)	4(2,8)	4(2,7)	5(2,9)	4(2,8)	4(2,7)
Age – M(sd)	60(16)	49(18)	49(16)	46(18)	54(19)	51(16)	65(17)	51(17)	53(18)	53(18)
Female	24929(67)	43757(52)	3474(53)	5678(54)	12664(54)	2936(81)	8974(63)	6301(61)	108713(57)	216287(57)
Cancer	3164(8)	4319(5)	301(5)	525(5)	1969(8)	261(7)	1673(12)	609(6)	12821(7)	24050(6)
CKD	4875(13)	5936(7)	529(8)	895(9)	2836(12)	436(12)	2574(18)	927(9)	19008(10)	28645(8)
Diabetes	4224(11)	6349(8)	564(9)	694(7)	2297(10)	259(7)	1934(12)	751(7)	17072(9)	26822(7)
CHD	3985(11)	5415(6)	403(6)	688(7)	2345(10)	242(7)	2082(15)	753(7)	15913(8)	25606(7)
COPD	2131(6)	2532(3)	200(3)	348(3)	1110(5)	105(3)	935(7)	269(3)	7630(4)	10428(3)
Stress	8006(21)	14598(17)	1239(19)	1880(18)	4505(19)	832(23)	2917(21)	2244(22)	36221(19)	57083(15)
Hypertension	14177(39)	25138(33)	1993(33)	2402(25)	6945(31)	1063(30)	6472(47)	3071(31)	61261(34)	112226(34)
Obesity	9710(29)	18926(27)	1837(34)	1792(20)	4339(21)	714(23)	3284(26)	2122(23)	42724(26)	69536(23)
Smoking	27738(76)	55278(69)	4364(70)	7236(82)	17927(80)	2419(69)	11124(81)	7365(74)	133451(73)	262379(76)
Alcohol	8060(24)	12930(19)	1103(20)	1826(21)	4195(22)	827(26)	3254(26)	1783(20)	33924(21)	62263(21)
AHT	19205(51)	28043(33)	2422(37)	3337(32)	10013(43)	1553(43)	8520(60)	4004(39)	77097(41)	128197(34)
Statins	9953(27)	13820(16)	1161(18)	1493(14)	5220(22)	621(17)	4585(32)	1749(17)	38602(20)	64919(17)
Hypnotics	5985(16)	9492(11)	934(14)	1366(13)	3361(14)	559(16)	2407(17)	1592(15)	25696(14)	37263(10)
NSAIDs	31894(85)	46984(56)	4477(69)	6089(58)	14115(61)	2513(70)	10080(71)	8571(83)	142723(66)	181991(48)
Steroids	16467(44)	14390(17)	1893(29)	3499(33)	7022(30)	1287(36)	8444(60)	2490(24)	55492(29)	54104(14)

Note: * - For ease of presentation some of the covariates data are not presented here. ± figures represent median and interquartile range. M-mean; sd-standard deviation; CD- Crohns disease, UC= ulcerative colitis, AS=ankylosing spondylitis, RA= rheumatoid arthritis, SLE=systemic lupus erythematosus. AHT=antihypertensive therapy; DMARDs= disease modifying anti-rheumatic drugs; NSADs= non-steroidal anti-inflammatory drugs; CKD= chronic kidney disease; COPD= chronic obstructive pulmonary disease; CHD= coronary heart disease.

Table 2. Adjusted hazard ratios (95%confidence interval) for depression and anxiety incidence among persons inflammatory disorders diagnosis compared to the matched comparison group.

		Age at diagnosis			
Depression incidence	Overall sample HR(95%CI)	<40 HR(95%CI)	40-49 HR(95%CI)	50-59 HR(95%CI)	≥60 HR(95%CI)
Psoriasis mild	1.30(1.26-1.35)	1.59(1.48-1.71)	1.32(1.20-1.45)	1.01(0.92-1.12)	0.88(0.81-0.95)
Psoriasis severe	1.71(1.52-1.93)	2.00(1.61-2.48)	1.77(1.39-2.24)	1.21(0.94-1.57)	0.87(0.66-1.13)
Rheumatoid arthritis	1.38(1.29-1.47)	2.40(2.07-2.79)	1.93(1.68-2.22)	1.40(1.23-1.59)	1.06(0.96-1.17)
Systemic lupus erythematosus	1.28(1.06-1.56)	1.27(0.91-1.78)	1.53(1.09-2.14)	1.02(0.68-1.54)	0.91(0.65-1.28)
Ankylosing spondylitis	1.44(1.30-1.60)	1.93(1.59-2.33)	1.62(1.30-2.01)	1.30(1.02-1.65)	1.07(0.87-1.30)
Systemic vasculitis	1.46(1.31-1.62)	2.52(1.98-3.20)	2.37(1.83-3.09)	1.73(1.37-2.20)	1.23(1.07-1.42)
Ulcerative colitis	1.39(1.29-1.49)	1.81(1.60-2.05)	1.31(1.09-1.56)	1.44(1.22-1.70)	0.96(0.84-1.09)
Crohn's disease	1.47(1.32-1.63)	1.84(1.55-2.19)	1.59(1.26-2.00)	1.28(0.99-1.65)	0.92(0.73-1.14)
Anxiety incidence					
Psoriasis mild	1.28(1.24-1.33)	1.51(1.40-1.63)	1.08(0.97-1.21)	1.03(0.93-1.15)	0.85(0.78-0.93)
Psoriasis severe	1.33(1.17-1.50)	1.40(1.10-1.80)	1.31(0.98-1.75)	1.04(0.77-1.41)	0.84(0.63-1.14)
Rheumatoid arthritis	1.10(1.03-1.18)	1.51(1.26-1.81)	1.20(1.01-1.43)	0.93(0.79-1.09)	0.80(0.71-0.90)
Systemic lupus erythematosus	1.28(1.06-1.55)	1.25(0.78-1.83)	1.61(1.07-2.42)	1.03(0.63-1.67)	0.78(0.49-1.22)
Ankylosing spondylitis	1.36(1.23-1.51)	1.54(1.25-1.90)	1.33(1.05-1.70)	1.32(1.03-1.70)	1.08(0.88-1.32)
Systemic vasculitis	1.19(1.07-1.32)	1.52(1.15-2.02)	1.45(1.04-2.02)	1.24(0.94-1.64)	1.01(0.86-1.18)
Ulcerative colitis	1.34(1.24-1.44)	1.57(1.35-1.83)	1.21(0.991.48)	0.94(0.76-1.17)	0.86(0.74-1.00)
Crohn's disease	1.35(1.21-1.50)	1.24(1.02-1.49)	0.97(0.73-1.28)	1.03(0.76-1.39)	0.78(0.61-1.00)

HR- hazard rate; CI- confidence interval. Adjusted for age, gender, deprivation, BP, BMI, smoking, alcohol, CHD, stroke, cancer, diabetes, cancer, dementia, epilepsy, CKD, liver disease, COPD, sleep disorders, AHT, statins, hypnotics, corticosteroids, NSAIDs, anti-diabetics.

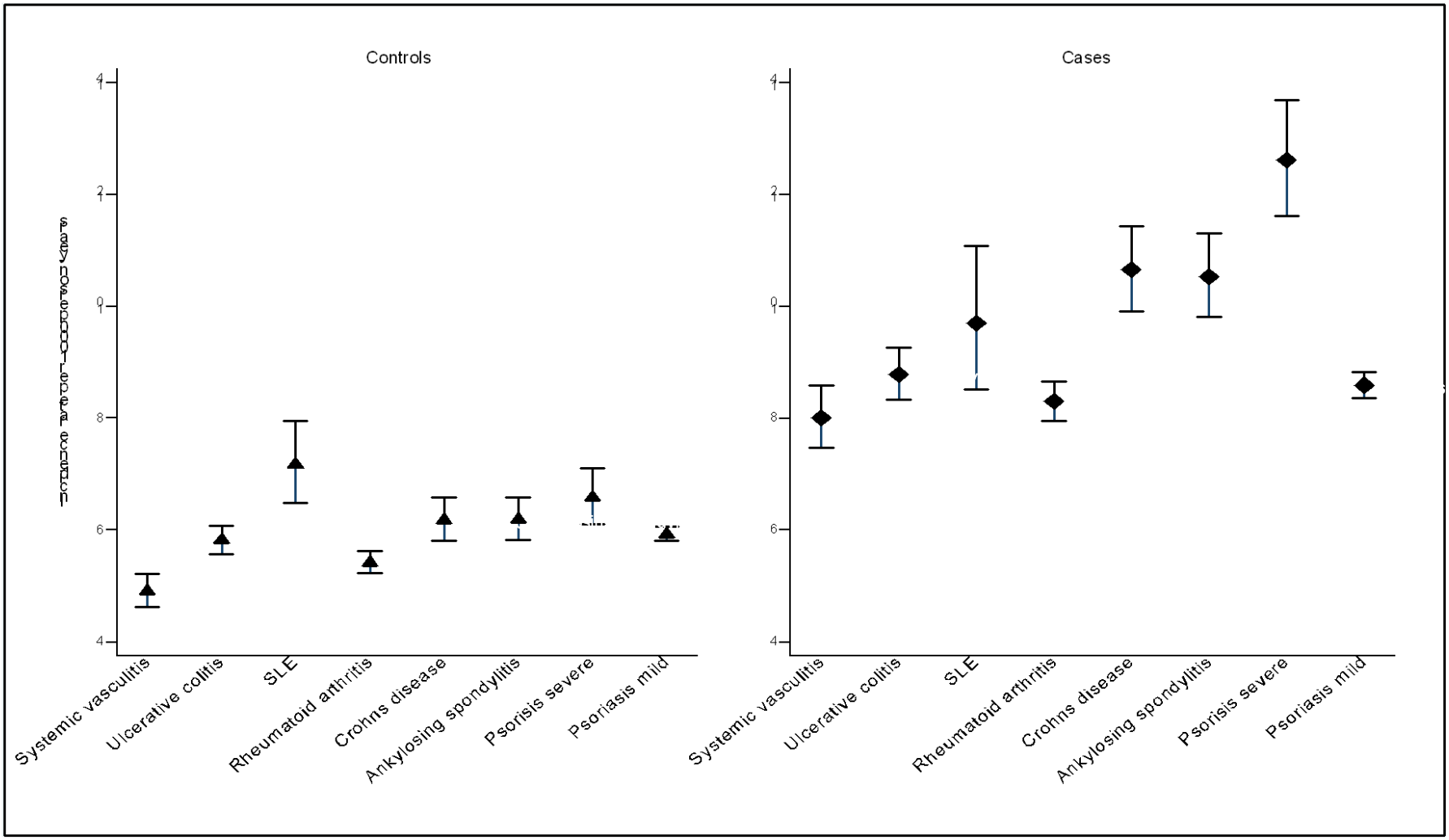

Figure 1 Incidence of depression by condition for participants with chronic inflammatory disorders and matched controls.

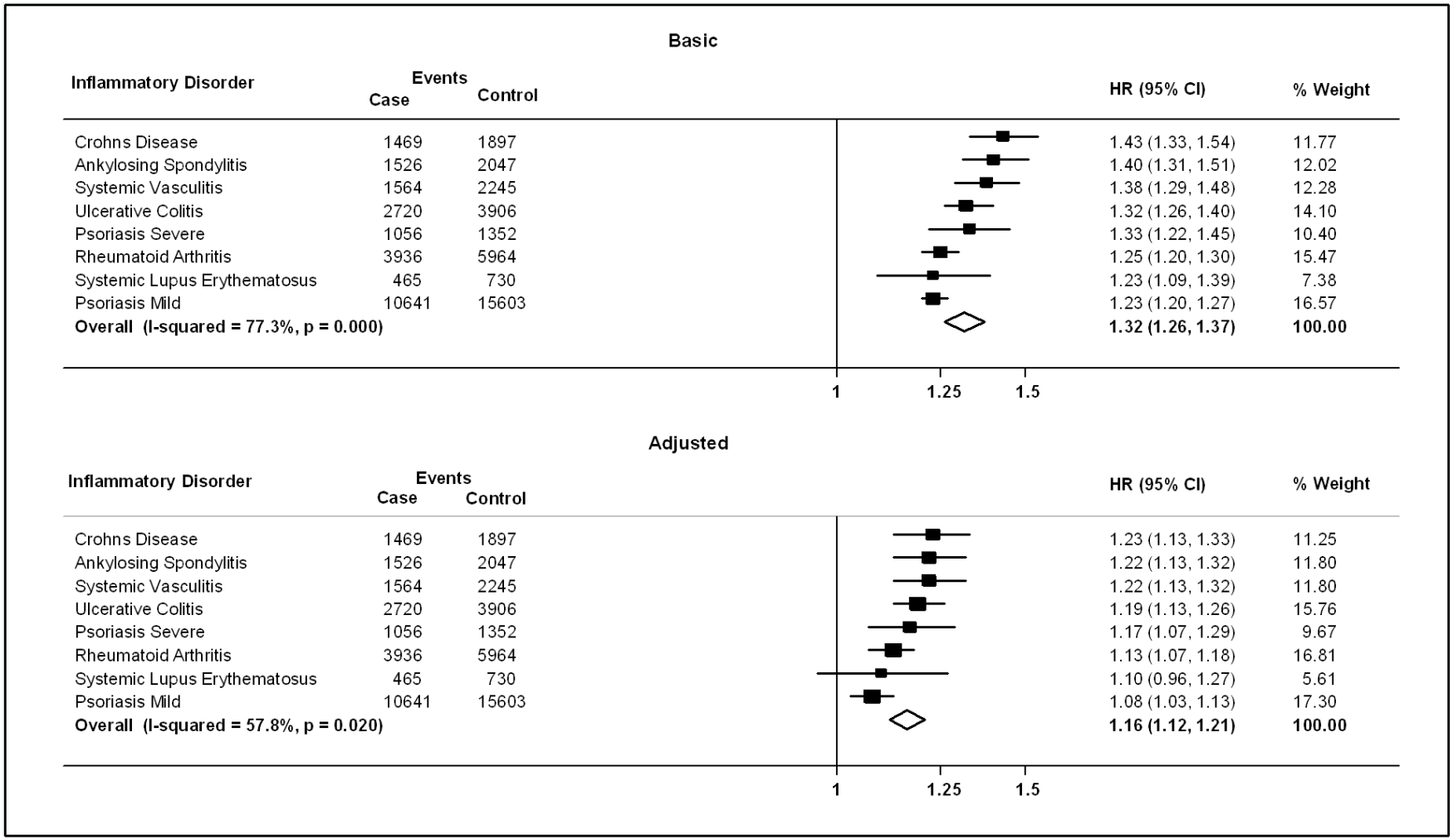

Figure 2. Forest plot displaying random-effects meta-analysis of the influence of specific inflammatory disorders on the incidence of multiple depression and anxiety outcomes. CI indicates confidence interval; HR, hazard rate. Basic - adjusted for age and gender. Adjusted – adjusted for age, gender, deprivation, BP, BMI, smoking, alcohol, CHD, stroke, cancer, diabetes, cancer, dementia, epilepsy, CKD, liver disease, COPD, sleep disorders, AHT, statins, hypnotics, corticosteroids, NSAIDs, anti-diabetics.

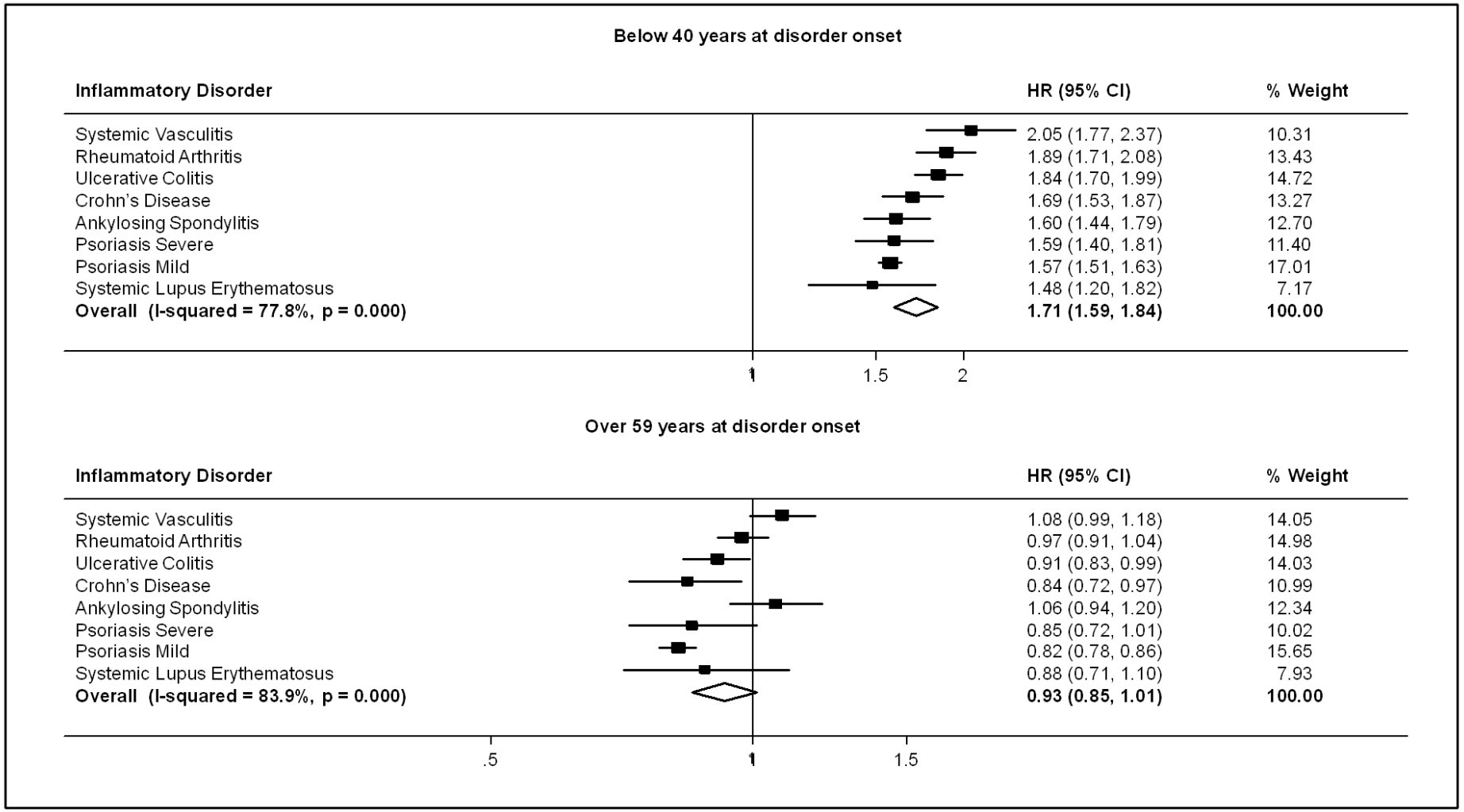

Figure 3 Forest plot displaying random-effects meta-analysis of the influence of age at inflammatory disorders onset on the incidence of multiple depression and anxiety. CI indicates confidence interval; HR, hazard rate. Adjusted for age, gender, deprivation, BP, BMI, smoking, alcohol, CHD, stroke, cancer, diabetes, cancer, dementia, epilepsy, CKD, liver disease, COPD, sleep disorders, AHT, statins, hypnotics, corticosteroids, NSAIDs, anti-diabetics.