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ORIGINAL ARTICLE

Depression and the risk of autoimmune disease: a nationally representative, prospective longitudinal study

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Background. Autoimmune diseases are associated with substantial morbidity and mortality, yet the etiology remains unclear. Depression has been implicated as a risk factor for various immune-related disorders but little is known about the risk of autoimmune disease. This study examined the association between depression and the risk of autoimmune disease, and investigated the temporal and dose-response nature of these relationships.

Method. A prospective population-based study including approximately 1.1 million people was conducted using linked Danish registries. Depression and autoimmune diseases were diagnosed by physicians and documented in medical records. In total, 145 217 individuals with depression were identified between 1995 and 2012. Survival analyses were used to estimate the relative risk of autoimmune disease among those with, compared to without, depression. Analyses were adjusted for gender, age, and co-morbid mental disorders.

Results. Depression was associated with a significantly increased risk of autoimmune disease [incidence rate ratio (IRR) 1.25, 95% CI 1.19–1.31], compared to those without a history of depression. Results suggest a general increased risk of autoimmune diseases following the onset of depression during first year (IRR 1.29, 95% CI 1.05–1.58), which remained elevated for the ensuing 11 years and beyond (IRR 1.53, 95% CI 1.34–1.76). Findings did not support a dose-response relationship.

Conclusions. Depression appears to be associated with an increased risk of a range of autoimmune diseases. Depression may play a role in the etiology of certain autoimmune conditions. If replicated, findings could highlight additional clinical implications in the treatment and management of depression. Future studies are needed to investigate the possible social, genetic, and neurobiological underpinnings of these relationships.

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Key words: Autoimmune disease, depression, epidemiology, humans, longitudinal studies, prospective studies.

Introduction

Autoimmune diseases (ADs) are common (4.5–7%), associated with significant threat to quality of life, and are responsible for substantial direct and indirect societal costs (Autoimmune Diseases Coordinating Committee, 2005; Miller *et al.* 2012). ADs are a group of chronic inflammatory diseases that develop as a result of the loss of immunological tolerance to self-antigens. ADs afflict specific target organs or multiple organ systems depending on the specific disorder (Anaya, 2012). Interactions between genetic and environmental factors are thought to be the main explanatory mechanisms for their susceptibility and onset (Miller *et al.* 2012). Still, current known genetic risk factors and environmental exposures are unable to fully explain the occurrence of these diseases.

The literature increasingly suggests a link between depression and physical health, particularly relating to disorders associated with dysfunction of the immune system (Penninx *et al.* 2013). For example, depression has been found to be associated with increased risk of the onset and progression of chronic diseases such as cardiovascular, neuroplastic, and neurodegenerative diseases (Penninx *et al.* 2013).

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Depression is one of the most common diseases globally: 6% of the population meet criteria for major depressive disorder (past year) and one in five individuals experiences a depressive episode during their lifetime (Alonso *et al.* 2004). As such, depression constitutes a major global problem that has profound social and economic consequences for both individuals and society (Alonso *et al.* 2004).

To date, few studies have examined the association between depression and ADs. In general, clinical AD patient populations tend to have higher rates of depression compared to those without ADs (Valtysdottir *et al.* 2000; Carta *et al.* 2002; Zyrianova *et al.* 2006; Nery *et al.* 2007; Gold & Irwin, 2009; Mitsonis *et al.* 2009; Inal *et al.* 2010; Sharma *et al.* 2011; Kirim *et al.* 2012; Benros *et al.* 2013; Giynas Ayhan *et al.* 2014; Schramm *et al.* 2014) and findings from epidemiologic community-based studies suggest an association between depression and some ADs (Pop *et al.* 1998; Degner *et al.* 2001; Carta *et al.* 2004; Engum, 2007; Maunder & Levenstein, 2008; Bachen *et al.* 2009; Baysal *et al.* 2011; Korczak *et al.* 2011; Vattakatuchery *et al.* 2011; Roy & Lloyd, 2012; Smith & Gerdes, 2012; van de Ven *et al.* 2012; Ananthakrishnan *et al.* 2013; Dominguez *et al.* 2013; Matcham *et al.* 2013; Palagini *et al.* 2013; Rotella & Mannucci, 2013; Dowlatshahi *et al.* 2014). Prior studies have primarily focused on the prevalence of depression among individuals with AD, yet there has been speculation that the relationship is likely to be bidirectional (Kiecolt-Glaser & Glaser, 2002; Miller *et al.* 2009; Baysal *et al.* 2011; Irwin & Cole, 2011; Benros *et al.* 2013; Dowlatshahi *et al.* 2014). Previous studies assessing the risk of ADs subsequent to depression onset are scarce and limited by various methodological constraints. These include: (1) the use of cross-sectional data which precludes an examination of the temporal relationship between depression and risk of ADs; (2) the relative rarity of some autoimmune conditions which limits the study of ADs in many investigations – apart from those that include extremely large sample sizes; and (3) the almost exclusive reliance on self-report measures of mental health and physical conditions, which are subject to misreport and questionable validity for some diseases, in most population-based studies.

In an effort to address the shortcomings of previous research, we conducted a nationwide cohort study using the longitudinal Danish registries to examine the association between depression and the risk of ADs. The aims of the current study were: (1) to examine the relationship between depression and the risk of a wide range of ADs; (2) to determine whether the timing of the onset of depression was predictive of the timing of AD incidence; and (3), to test for the presence of a dose-response relationship.

Method

Study population

In this prospective nationwide register-based study the dataset was gathered through the linkage of several Danish registries that cover the entire population (5.6 million people). Each individual's general personal information (e.g. age, gender, and history of municipal residency) and full treatment history – including all somatic and psychiatric diagnoses – was linked across The Danish Civil Registration System (DCRS), the Danish National Hospital Register (DNHR), and the Danish Psychiatric Central Research Register (DPCRR) (Munk-Jorgensen & Mortensen, 1997; Andersen *et al.* 1999; Pedersen *et al.* 2006; Mors *et al.* 2011; Nguyen-Nielsen *et al.* 2013). The ICD-10 was introduced in 1994, and therefore the current study period relied on data from 1995 and onward in order to minimize the risk of inconsistencies due to the use of different diagnostic systems over time (Lundberg *et al.* 2013).

Initially, we identified 145 217 individuals with a primary diagnosis of depression for the study cohort (see variable criteria below). Each individual was then match-controlled with six other individuals from the Danish population, with no record of depression, on gender, age (i.e. date of birth within 6 months of range) and latest municipality of residence (through the DCRS). Individuals were excluded if they had a diagnosis of AD (see variable criteria below) documented at any time prior to the study period. The study population therefore was free of any prior history of AD, ensuring that only incident AD could be examined as an outcome. Collectively, the study population consisted of 1 016 519 individuals.

Measures

Depression

For this study, depression was defined as the presence of a primary diagnosis of depression in the medical record from 1995 through 2012 (Munk-Jørgensen *et al.* 2014). Depression diagnoses included were ICD-10: F32-F33, i.e. only depressive episode and recurrent depressive disorder. No other mood disorders (e.g. bipolar disorder) were included. All diagnoses were made by physicians during clinical contact in psychiatric emergency, inpatient, and outpatient treatment settings. The onset of depression was defined as the date of initial clinical contact in which a diagnosis of depression was recorded (identified through the DPCRR). A 'primary diagnosis' was defined as the diagnosis that is the primary cause of treatment contact as determined by the treating physician. Therefore, any individuals with a secondary diagnosis of depression

were excluded from the study in an effort to maintain consistency in the severity of depression. Both start- and end-date of clinical contact for the treatment of depression were recorded through the registry and used for calculating number of depressive episodes as an estimate of depression chronicity. A depressive episode was considered remitted if clinical contact, including both inpatient and outpatient visits, ceased for at least 6 consecutive months (i.e. a period of 6 months from the end-date of a treatment contact to the start-date of subsequent treatment contact). Clinical contact, following any period of time after the 6 consecutive months of no contact, was then counted as a separate depressive episode.

Autoimmune disease

The onset of AD was estimated by the date of the first clinical contact in which an AD was diagnosed by a physician in a treatment setting and documented in the medical record (through the DNHR). The following ADs (using their respective ICD-10 codes) were included (Eaton *et al.* 2007, 2010): Ankylosing spondylitis (M45), Autoimmune thyroiditis (E06.3), Celiac disease (K90.0), Crohn's disease (K50), Idiopathic thrombocytopenic purpura (D69.3), Iridocyclitis (H20), Multiple sclerosis (G35), Primary adrenocortical insufficiency (Addison's) (E27.1), Psoriasis vulgaris (L40.0), Rheumatoid arthritis (M05, M06), Sjögren's syndrome (M35.0), Systemic lupus erythematosus (M32), Thyrotoxicosis (Graves' disease) (E05.0), Type 1 diabetes mellitus (E10), Ulcerative colitis (K51).

Statistical approach

Individuals were followed from the first-time clinical contact for depression until either their first recorded diagnosis of an AD, death, or the end of the study period (whichever occurred first). Survival analyses were used to address each aim. Cox proportional hazard regressions for calculating incidence rates were performed for each analysis in this study. To measure relative risk, incidence rate ratios (IRRs) with accompanying 95% confidence intervals (CIs) based on Wald statistics were calculated using Stata v. 13 (StataCorp, 2013).

In fully adjusted models, data were stratified by age, gender and psychiatric co-morbidities (e.g. anxiety disorder, substance use disorders). Psychiatric co-morbidity was treated as a binary variable for the presence/absence of any lifetime psychiatric disorder (other than depression) (based on ICD-8: 290–315 except 302 for the time period before 1994 and ICD-10: F:00–99 except F32-F33).

To address aims (1) and (3), the incidence rates and IRR on each specific AD were calculated. In the event of an AD diagnosis, an individual would subsequently be removed from the population at risk for that given AD at the date of diagnosis though they remained in the risk pool to acquire other ADs during the remaining study period.

To address aim (2), we identified the number of years from the onset of the first depressive episode and/or start of tracing the non-depressed matched individuals up to the diagnosis of AD. Incidence rates and IRR for each year were then calculated following onset of depression. In the event of an AD diagnosis, an individual would subsequently be removed from the population at risk for all ADs at the date of the first documentation of any AD.

To address aim (3), the number of experienced depressive episodes was dichotomized into one or two or more episodes of depression and incidence rates and IRRs were then accordingly calculated.

In supplementary analyses, we conducted analyses stratified by age and gender as well as by grouping of ADs based on their similar immunopathologic features (Dube *et al.* 2009).

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Descriptive measures

This study included 1 016 519 individuals followed up to a total of 7 337 598 million person-years from 1995 through 2012. The mean age upon study entry was 46.7 (S.D. = 20.6) years and a slight majority were female (63.9%) (see Table 1). In total, 86 689 (59.7%) individuals with a primary diagnosis of depression and 85 331 (9.8%) individuals without depression had a psychiatric disorder (other than depression). Table 1 provides additional information on the distribution of these psychiatric conditions in categories developed in previous studies (Pedersen *et al.* 2014).

Of the 145 217 individuals with depression, 120 602 (83%), 18 760 (13%), 3752 (2.6%), and 2103 (1.4%) experienced 1, 2, 3, and $\geqslant 4$ depressive episodes, respectively. We identified 19 904 (2.0%) individuals with a diagnosis of AD during the study period; 70.5% were female and 3% ($n = 597$) had multiple AD diagnoses. The six most frequent ADs (which comprised 87.4% of all diagnosed ADs) were: type 1 diabetes mellitus, rheumatoid arthritis, ulcerative colitis, Graves' disease, multiple sclerosis, and Crohn's

Table 1. *Age, gender and psychiatric disorders among individuals with and without depression*

	Depression *N*		No depression *N*		Total *N*	%
Gender						
Female	92 714		556 284		648 998	63.85
Male	52 503		315 018		367 521	36.15
Total	145 217		871 302		1 016 519	100.00
Age, years						
Mean	46.7		46.7		46.7	
S.D.	20.6		20.6		20.6	
Age grouping at study entry, years						
<29	36 015		216 093		252 108	24.8
30–49	49 239		295 431		344 670	33.9
50–69	33 254		199 524		232 778	22.9
⩾70	26 709		160 254		186 963	18.4
Total	145 217		871 302		1 016 519	100.0
Age grouping at AD onset, years						
<29	361		2166		2527	12.7
30–49	1123		6735		7858	39.5
50–69	1003		6019		7022	35.3
⩾70	357		2140		2497	12.6
Total	2843		17 061		19 904	100.0
Number of ADs						
1	3100		16 207		19 307	97.0
2	112		465		577	2.90
3	4		16		20	0.10
Total	3216		16 688		19 904	100.0
Psychiatric co-morbidities[a]	*N*	%	*N*	%	*N*	%
Any psychiatric disorder[b]	86 689	59.7	85 331	9.8	173 020	16.9
Diagnoses[c]	*N*	%[d]	*N*	%[d]	*N*	%[d]
Organic, including symptomatic, mental disorders[e]	11 829	13.6	20 707	24.3	32 536	18.9
Substance use disorders	19 629	22.6	15 974	18.7	35 603	20.7
Schizophrenia and related disorders	18 061	20.8	14 267	16.7	32 328	18.8
Bipolar disorders	7919	9.1	1115	1.3	9034	5.3
Neurotic, stress-related, and somatoform disorders[f]	54 842	63.3	37 230	43.6	92 072	53.5
Eating disorders	3012	3.5	3885	4.6	6897	4.0
Specific personality disorders	24 854	28.7	14 341	16.8	39 195	22.8
Pervasive developmental disorders	1237	1.4	1422	1.7	2659	1.5
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	14 565	16.8	9250	10.8	23 815	13.8

[a] The category grouping of psychiatric disorders are adapted from Pedersen *et al.* (2014).

[b] Individuals had at least one psychiatric disorder (other than depression).

[c] An individual could have more than one other psychiatric diagnosis.

[d] Percentages of the individuals with any other psychiatric disorders.

[e] These diagnoses include disorders such as dementia; delirium; mental disorders due to brain damage, dysfunction or physical disease and; personality and behavioral disorders due to brain disease, damage or dysfunction.

[f] These diagnoses include disorders such as anxiety disorders; obsessive-compulsive disorders; reaction to severe stress, and adjustment disorders; dissociative disorders and; somatoform disorders.

Table 2. *Incidence rate ratios (IRRs) for depression and risk of autoimmune disease*

			Depression							
	Comparisons				Crude		Model 1[a]		Model 2[b]	
Autoimmune disease	Cases	IR[c]	Cases	IR[c]	IRR*	95%CI	IRR*	95% CI	IRR*	95% CI
Any autoimmune disease[d]	14 331	228.0	2780	275.7	**1.23**	1.18–1.28	**1.24**	1.19–1.29	**1.25**	1.19–1.31
Blood										
Idiopathic thrombocytopenic purpura	125	2.0	27	2.7	1.38	0.91–2.10	1.45	0.94–2.23	**1.85**	1.10–3.11
Endocrine system										
Thyrotoxicosis, Graves' disease	1683	26.6	281	27.7	1.07	0.94–1.21	1.07	0.94–1.21	1.05	0.90–1.22
Autoimmune thyroiditis (Hashimoto's)	170	2.7	38	3.8	1.41	1.00–2.01	1.33	0.93–1.89	1.27	0.82–1.97
Type 1 diabetes mellitus	2928	46.4	723	71.4	**1.57**	1.44–1.70	**1.58**	1.45–1.71	**1.47**	1.33–1.63
Primary adrenocortical insufficiency (Addison's)	94	1.5	28	2.8	**1.89**	1.24–2.89	**1.96**	1.27–3.01	**2.33**	1.36–3.98
Nervous system										
Multiple sclerosis	1492	23.6	317	31.3	**1.34**	1.20–1.52	**1.32**	1.17–1.49	**1.46**	1.26–1.69
Eye										
Iridocyclitis	147	2.3	27	2.7	1.16	0.77–1.75	1.12	0.74–1.70	1.01	0.61–1.66
Digestive system										
Crohn's disease	1252	19.8	275	27.1	**1.39**	1.22–1.58	**1.38**	1.21–1.57	**1.36**	1.16–1.60
Ulcerative colitis	2069	32.8	339	33.5	1.04	0.93–1.16	1.04	0.93–1.12	1.17	0.98–1.29
Celiac disease	328	5.2	67	6.6	1.29	0.99–1.68	1.28	0.98–1.67	1.12	0.81–1.53
Skin										
Psoriasis vulgaris	520	8.2	124	12.2	**1.51**	1.24–1.84	**1.53**	1.26–1.87	**1.45**	1.13–1.85
Musculoskeletal system and connective tissue										
Rheumatoid arthritis	3083	48.8	444	43.8	0.92	0.84–1.02	0.96	0.87–1.06	1.01	0.90–1.44
Systemic lupus erythematosus	285	4.5	74	7.3	**1.66**	1.28–2.14	**1.63**	1.26–2.11	**1.38**	1.00–1.91
Sjögren syndrome	182	2.9	46	4.5	**1.62**	1.18–2.25	**1.63**	1.17–2.26	1.51	0.99–2.28
Ankylosing spondylitis	428	6.8	73	7.2	1.08	0.85–1.39	1.06	0.82–1.36	1.14	0.85–1.53

CI, Confidence interval.
[a] Adjusted for gender and age.
[b] Adjusted for gender, age, and psychiatric co-morbidities.
[c] Incidence rates (IR) per 100000 person-years.
[d] All of the autoimmune diseases below.
*Boldface is $p < 0.05$ and underlined is $p < 0.01$.

disease. For the entire study population, the number of these cases was 4374 (22.0%), 4029 (20.2%), 2887 (14.5%), 2174 (10.9%), 2095 (10.5%), and 1834 (9.2%) respectively.

Association between depression and ADs

Overall, a history of depression was significantly associated with risk of 'any AD' (IRR 1.25, CI 1.19–1.31, see Table 2). Across the analyses, depression was significantly associated with eight out of the 15 examined ADs. In results from the fully adjusted model (model 2), depression remained significantly associated with an increased risk of idiopathic thrombocytopenic purpura (IRR 1.85, 95% CI 1.10–3.11), type 1 diabetes mellitus (IRR 1.47, 95% CI 1.33–1.63), Addison's disease (IRR 2.33, 95% CI 1.36–3.98), multiple sclerosis (IRR 1.46, 95% CI 1.26–1.69), Crohn's disease (IRR 1.36, 95% CI 1.16–1.60), psoriasis vulgaris (IRR 1.45, 95% CI 1.13–1.85), and systemic lupus erythematosus (IRR 1.38, 95% CI 1.00–1.91).

Time-related associations on the onset of depression and subsequent risk of ADs

Our findings suggest that the susceptibility of developing an AD was relatively consistent over time following the onset of depression (See Table 3). Specifically, no notable difference in the risk of AD was found between the 1st and 11th years following the onset of

Table 3. *Incidence rate ratios (IRRs) of any autoimmune disease since the time of onset of depression*

Time since onset of first-time depression (years) and since start date of tracing for non-depressed	Comparisons		Depression[a]			
	Cases	IR[b]	Cases	IR[b]	IRR*	95% CI
<1	633	1706.7	152	2279.8	**1.29**	1.05–1.58
1	609	586.3	163	882.7	**1.49**	1.22–1.81
2	635	370.7	135	442.9	1.05	0.84–1.32
3	561	249.9	145	364.9	**1.48**	1.19–1.83
4	584	221.9	136	292.8	**1.31**	1.04–1.64
5–10	3009	129.9	643	165.1	**1.31**	1.18–1.45
⩾11	1794	56.3	402	83.9	**1.53**	1.34–1.76

CI, Confidence interval.
[a] Adjusted for gender, age and psychiatric co-morbidities.
[b] Incidence rates (IR) per 100000 person-years.
*Boldface is $p < 0.05$ and underlined is $p < 0.01$

depression (IRR 1.29, 95% CI 1.05–1.58 and IRR 1.53, 95% CI 1.34–1.76, respectively). The risk of AD remained increased throughout all years after the onset of depression, except during the 2nd year, in which the association was not significant (IRR 1.05, 95% CI 0.84–1.32).

Dose-response relationship between number of depressive episodes and risk of ADs

The risk of 'any type of AD' was not found to increase in a dose-response relationship with the number of depressive episodes (see Table 4). One depressive episode was significantly associated with a higher risk of developing any AD (IRR 1.26, 95% CI 1.19–1.33) but risk was not more elevated as a function of having ⩾2 depressive episodes (IRR 1.20, 95% CI 1.05–1.38).

Age- and gender-stratified analyses

There was no significant gender difference in the relationship between depression and risk of ADs (see Supplementary Table S1). The relationship between depression and risk of ADs appeared to be more prominent among individuals aged <50 years, compared to those aged ⩾50 years (see Supplementary Table S1). All associations were significant for those aged <50 years while there was only one significant finding in the 50–69 years age group (IRR 1.20, 95% CI 1.10–1.31).

Depression and the risk of ADs when grouping by similar immunopathology

Depression was significantly associated with both T-helper 1 (Th1) and mixed Th1/T-helper 2 (Th2) in both the analyses of 1 and ⩾2 depressive episodes (see Supplementary Table S2). The IRR increased within both Th1 and mixed Th1/Th2 at one depressive episode from IRR 1.30 (95% CI 1.20–1.40) and IRR 1.33 (95% CI 1.19–1.49), respectively, to IRR 1.46 (95% CI 1.28–1.67) and IRR 1.45 (95% CI 1.21–1.73), respectively, when having experienced ⩾2 depressive episodes. Only one depressive episode was significantly associated with Th2 and Th2 rheumatic subgroups (the latter borderline significant) and results did not show any positive correlation between the number of depressive episodes and an increased risk of AD within these two immunopathology groupings.

Discussion

This study was representative of the Danish population and included all individuals with a diagnosis of depression from 1995 through 2012. Using this approach, we had a unique opportunity to conduct prospective analyses on the incidence of ADs among those with and without depression (Munk-Jorgensen & Ostergaard, 2011). This study has four main findings. First, a history of at least one episode of depression was associated with a subsequently increased overall risk of the incidence of any AD. Second, depression was associated with increased risk of the onset of a wide range of specific ADs, though level of risk differed somewhat by type of AD. Third, the increased risk of ADs following the onset of depression was consistent over time. Fourth, there was not a clear dose-response relationship between depression and risk of all types of AD. These findings offer evidence of a possible link between depression and the subsequent risk of AD and suggest that the influence of depression tends to impact specific types of AD. Below,

Table 4. *Incidence rate ratios (IRRs) for depressive episodes and risk of autoimmune diseases*

	1 Depressive episode				⩾2 Depressive episodes			
			Model 2[a]				Model 2[a]	
Autoimmune disease	Cases	IR[b]	IRR*	95% CI	Cases	IR[b]	IRR*	95% CI
Any autoimmune disease[c]	2328	267.8	**1.26**	1.19–1.33	452	324.8	**1.20**	1.05–1.38
Blood								
Idiopathic thrombocytopenic purpura	25	2.9	**2.03**	1.19–3.45	–		–	
Endocrine system								
Thyrotoxicosis, Graves' disease	230	26.3	1.07	0.91–1.26	51	36.5	0.95	0.65–1.41
Autoimmune thyroiditis (Hashimoto's)	31	3.6	1.23	0.77–1.97	7	5.0	1.57	0.51–4.80
Type 1 diabetes mellitus	605	69.3	**1.46**	1.31–1.62	118	84.4	**1.57**	1.18–2.10
Primary adrenocortical insufficiency (Addison's)	25	2.9	**2.46**	1.40–4.32	–		–	
Nervous system								
Multiple sclerosis	264	30.2	**1.48**	1.27–1.74	53	37.9	1.30	0.88–1.92
Eye								
Iridocyclitis	26	3.0	1.12	0.68–1.86	–		–	
Digestive system								
Crohn's disease	235	26.9	**1.37**	1.15–1.63	40	28.6	1.31	0.82–2.07
Ulcerative colitis	283	32.4	1.13	0.98–1.31	56	40.0	1.02	0.70–1.49
Celiac disease	52	6.0	1.08	0.76–1.53	15	10.7	1.28	0.59–2.80
Skin								
Psoriasis vulgaris	105	12.0	**1.46**	1.13–1.89	19	13.6	1.53	0.72–3.26
Musculoskeletal system and connective tissue								
Rheumatoid arthritis	377	43.2	1.06	0.93–1.20	67	47.9	0.80	0.57–1.12
Systemic lupus erythematosus	59	6.8	1.26	0.89–1.78	15	10.7	**3.10**	1.16–8.26
Sjögren's syndrome	38	4.4	1.43	0.92–2.22	8	5.7	2.88	0.75–11.00
Ankylosing spondylitis	59	6.8	1.09	0.79–1.49	14	10.0	1.60	0.70–3.67

[a] Adjusted for gender, age and psychiatric co-morbidities.
[b] Incidence rates (IR) per 100000 person-years.
[c] All of the ADs below.
*Boldface is $p < 0.05$ and underlined is $p < 0.01$.

the aforementioned findings will be discussed in the context of existing literature and suggestions for future research and clinical implications will be provided.

It is not possible to determine the mechanism of the association between depression and ADs based on this study. However, a plausible biological mechanism explaining the association between depression and AD could be the bidirectional interplay of the central nervous and immune systems. Psychological distress (e.g. depressive symptoms) can have a prolonged impact on neuroendocrine pathways such as the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. These pathways can both directly and indirectly regulate immune functioning (e.g. through changes in gene transcription activity in immunocytes). Following prolonged stimulation of these connections, the immune system may become dysregulated, contributing to the development and progression of autoimmune pathologies (Kiecolt-Glaser & Glaser, 2002; Glaser & Kiecolt-Glaser, 2005; Miller *et al.* 2009; Irwin & Cole, 2011; Voinov *et al.* 2013).

Previous literature suggests a bidirectional association between depression and the immune system with studies documenting a link between prior AD and increased risk of the subsequent onset of depression (Kiecolt-Glaser & Glaser, 2002; Miller *et al.* 2009; Baysal *et al.* 2011; Irwin & Cole, 2011; Benros *et al.* 2013; Dowlatshahi *et al.* 2014). For example, depression has been linked with increased inflammatory markers and depression risk alleles have been found to be associated with regulating genes of the immune response. Likewise, a recent Danish register study has shown that autoimmune disease is associated with an increased risk of depression and a meta-analysis suggests that anti-inflammatory treatment decreases depressive symptoms (Miller *et al.* 2009; Raison & Miller, 2012; Benros *et al.* 2013; Köhler *et al.* 2014). In addition, recent studies have also found an increased

risk of ADs among individuals with schizophrenia and eating disorders, which may provide further support for a bidirectional link between psychological disturbance (i.e. central nervous system) and the immune system (Benros *et al.* 2014; Raevuori *et al.* 2014).

Our subanalysis on grouping of ADs based on similar immunopathology suggested depression was more strongly associated with a higher risk of ADs characterized as immune Th1-type and/or mixed Th1/Th2-type responses. Of note, depression was not significantly associated with the rheumatic disorder subgroup. This may suggest that depression has a somewhat specific influence on the immune system, and thus these analyses could have the potential to generate new opportunities for future research.

We did not find a specific period of increased risk of AD following the onset of depression. Instead, our results suggest a general increased risk of AD any time after the onset of depression. The reason for this general increased risk over time is unclear. It is conceivable that the consistency in the increased risk over time could be explained either by differences in the time it takes for individuals in the population to build up an allostatic load of depression burden that reaches an AD onset 'threshold' or it could reflect differences in such thresholds of onset between the different ADs as well as differences in the course of development of ADs (McEwen, 2007). Further, it is possible that the actual onset of some cases of depression may have occurred many months/years prior to being diagnosed in a treatment setting. Alternatively, a diagnosis of AD may be delayed in some cases (e.g. because of sometimes long periods of undetected illness) further confounding an analysis of temporality. Another possibility is that an interaction of depression and stressful life events (e.g. divorce, death, job loss) could also account for the emergence of AD whereby the immune system – already enervated by the onset of depression – is further weakened by acute stress (Pace *et al.* 2006; Irwin & Miller, 2007), triggering the onset of AD. We could not examine stressful life events in the current study. Future research that can clarify the time relation between these onsets, possibly by improved and strictly defined time measures of depression and AD and taking into account environmental and social factors and events, is needed. Moreover, these results also suggest that the actual clinical contact, following the onset of depressive symptoms, does not seem responsible for the association of a higher risk of AD, nor does it appear that ADs were simply cases that were identified late, as the association between depression and ADs did not substantially differ over time (i.e. Berkson's bias).

Our findings did not suggest a general dose-response relationship between the number of depressive episodes and the risk of ADs. When analyses were stratified by age, the risk of ADs increased somewhat with the number of depressive episodes among individuals aged <50 years. Although findings are mixed, previous research has shown that HPA axis responses to stress may be more sensitive in younger as compared with older adults (Kudielka *et al.* 2004). Thus, age may play an important role in the differential activation of the HPA axis following the onset of depressive symptoms. In turn, the immune functioning of younger adults may be more prone to dysregulation than that of older adults, increasing the subsequent risk of autoimmune disease. It is also possible that the impact of depression is not deterministic but rather influences the risk in a stochastic manner, which would not necessarily be reflected in dose-response analyses.

A possible explanation for the lack of a clear dose-response relationship could be attributable to methodological issues related to our definition of depression chronicity. In addition, small cell sizes in many cases compromised our ability to calculate reliable estimates for several specific ADs. Future studies that employ different methods may be able to better assess frequency, duration, and severity of depression, which could help shed light on whether and to what degree the severity and persistence of depression influences the risk of AD.

The herein reported findings could have a number of potential implications for the understanding and management of depression. For example, individuals with depressive symptoms may benefit from further evaluation for AD, where earlier detection and medical intervention can reduce the influence of AD on both short-term and long-term health (such as diabetes). Moreover, increased awareness of the potentially increased risk of developing AD associated with depression would be important in treatment for both medical and psychiatric institutions. Overall, the present findings underpin the need to diagnose and successfully treat depression in primary- and secondary-care contexts, as this would not only diminish the significant burden of suffering due to depression itself, but could also potentially reduce the risk of somatic diseases.

Several limitations should be noted when interpreting the results of this study. First, our assessment of the severity of depression was quite limited. This is a key limitation of registry data as there is limited information on clinical heterogeneity of a particular diagnosed condition. Depression can present in a wide variety of severity and persistence and we attempted to restrict the cases to those that met a minimum severity criteria by only including those with a primary diagnosis of depression (Byrne *et al.* 2005; Parker,

2005; Munk-Jørgensen *et al.* 2014). No prior studies have systematically examined the validity or reliability of the range of depression diagnoses in the DPCRR, yet one study has validated single episode depression with good results (Bock *et al.* 2009; Mors *et al.* 2011). In the study by Bock *et al.* a total of 75.4% of 399 patients with a register diagnosis of a single depressive episode received the same diagnosis following a SCAN interview (82.8% for severe type of a single depression, 76.0% for moderate type of a single depression and 65.2% for mild type of a single depression). Second, estimates predict that only a minority of those with depression are ever seen in psychiatric treatment settings (Marcus & Olfson, 2010) therefore it is likely that those who are seen have at least a more moderate-severe depression. As such, some individuals within the comparison group may have had unreported depressive symptoms or mild depression, suggesting that our results may be rather conservative estimates. Moreover, misclassification of some AD cases is also likely, though there are unlikely to be systematic differences in this between cases and controls (Eaton *et al.* 2006). Future studies that can examine the roles of medication for both depression and somatic disorders in the association between depression and AD would be useful. Last, we were unable to adjust for various potential confounding factors (e.g. cigarette smoking, obesity), which could confound these associations (Autoimmune Diseases Coordinating Committee, 2005; van Gool *et al.* 2007), as the registers do not sufficiently capture this information. For example, in some studies smoking has been shown to be protective against ulcerative colitis while it has been associated with increased risk for Crohn's disease (van der Heide *et al.* 2011). As depression is known to be associated with smoking (Fergusson *et al.* 2003; Boden *et al.* 2010; Bakhshaie *et al.* 2015), future studies that include such information are needed to begin to understand the potential pathways underlying these associations.

In sum, depression appears to be associated with increased risk of subsequent diagnosis of AD, compared to those without a history of depression. The risk of AD onset was elevated following depression and this increased risk did not appear to be confined to a limited period of time following depression onset nor was it dependent on a specific 'dose' or severity of depression. In conclusion, our results provide initial data suggesting that depression may play a role in the etiology of certain autoimmune conditions. As this is the first longitudinal study to examine the relationship between depression and the subsequent risk of ADs as a group, these findings need to be replicated and further explored. If replicated in clinical studies, this may suggest additional risk for individuals with depressive disorders.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715001488.

Declaration of Interest

None.

References

Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro JM, Katz SJ, Kessler RC, Kovess V, Lepine JP, Ormel J, Polidori G, Russo LJ, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman MA, Codony M, Domingo-Salvany A, Ferrer M, Joo SS, Martinez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacin C, Romera B, Taub N, Vollebergh WA, EsemeD/Mhedea Investigators ESotEoMDP (2004). Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica* **109** (Suppl. 420), 21–27.

Ananthakrishnan AN, Khalili H, Pan A, Higuchi LM, de Silva P, Richter JM, Fuchs CS, Chan AT (2013). Association between depressive symptoms and incidence of Crohn's disease and ulcerative colitis: results from the Nurses' Health Study. *Clinical Gastroenterology and Hepatology* **11**, 57–62.

Anaya JM (2012). Common mechanisms of autoimmune diseases (the autoimmune tautology). *Autoimmunity Reviews* **11**, 781–784.

Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH (1999). The Danish National Hospital Register. A valuable source of data for modern health sciences. *Danish Medical Bulletin* **46**, 263–268.

Autoimmune Diseases Coordinating Committee (2005). *Progress in Autoimmune Diseases Research: Report to Congress*. US Department of Health and Human Services, Rockville, MD.

Bachen EA, Chesney MA, Criswell LA (2009). Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. *Arthritis and Rheumatism* **61**, 822–829.

Bakhshaie J, Zvolensky MJ, Goodwin RD (2015). Cigarette smoking and the onset and persistence of depression among adults in the United States: 1994–2005. *Comprehensive Psychiatry* **60**, 142–148.

Baysal O, Durmus B, Ersoy Y, Altay Z, Senel K, Nas K, Ugur M, Kaya A, Gur A, Erdal A, Ardicoglu O, Tekeoglu I, Cevik R, Yildirim K, Kamanli A, Sarac AJ, Karatay S, Ozgocmen S (2011). Relationship between psychological status and disease activity and quality of life in ankylosing spondylitis. *Rheumatology International* **31**, 795–800.

Benros ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB (2014). A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. *American Journal of Psychiatry* **171**, 218–226.

Benros ME, Waltoft BL, Nordentoft M, Ostergaard SD, Eaton WW, Krogh J, Mortensen PB (2013). Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. *JAMA Psychiatry* **70**, 812–820.

Bock C, Bukh J, Vinberg M, Gether U, Kessing L (2009). Validity of the diagnosis of a single depressive episode in a case register. *Clinical Practice and Epidemiology in Mental Health* **5**, 4.

Boden JM, Fergusson DM, Horwood LJ (2010). Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. *British Journal of Psychiatry* **196**, 440–446.

Byrne N, Regan C, Howard L (2005). Administrative registers in psychiatric research: a systematic review of validity studies. *Acta Psychiatrica Scandinavica* **112**, 409–414.

Carta MG, Hardoy MC, Boi MF, Mariotti S, Carpiniello B, Usai P (2002). Association between panic disorder, major depressive disorder and celiac disease: a possible role of thyroid autoimmunity. *Journal of Psychosomatic Research* **53**, 789–793.

Carta MG, Loviselli A, Hardoy MC, Massa S, Cadeddu M, Sardu C, Carpiniello B, Dell'Osso L, Mariotti S (2004). The link between thyroid autoimmunity (antithyroid peroxidase autoantibodies) with anxiety and mood disorders in the community: a field of interest for public health in the future. *BMC Psychiatry* **4**, 25.

Degner D, Meller J, Bleich S, Schlautmann V, Ruther E (2001). Affective disorders associated with autoimmune thyroiditis. *Journal of Neuropsychiatry and Clinical Neurosciences* **13**, 532–533.

Dominguez PL, Han J, Li T, Ascherio A, Qureshi AA (2013). Depression and the risk of psoriasis in US women. *Journal of the European Academy of Dermatology and Venereology* **27**, 1163–1167.

Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T (2014). The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. *Journal of Investigative Dermatology* **134**, 1542–1551.

Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB (2009). Cumulative childhood stress and autoimmune diseases in adults. *Psychosomatic Medicine* **71**, 243–250.

Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, Mortensen PB (2006). Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. *American Journal of Psychiatry* **163**, 521–528.

Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB (2010). Autoimmune diseases, bipolar disorder, and non-affective psychosis. *Bipolar Disorders* **12**, 638–646.

Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB (2007). Epidemiology of autoimmune diseases in Denmark. *Journal of Autoimmunity* **29**, 1–9.

Engum A (2007). The role of depression and anxiety in onset of diabetes in a large population-based study. *Journal of Psychosomatic Research* **62**, 31–38.

Fergusson DM, Goodwin RD, Horwood LJ (2003). Major depression and cigarette smoking: results of a 21-year longitudinal study. *Psychological Medicine* **33**, 1357–1367.

Giynas Ayhan M, Uguz F, Askin R, Gonen MS (2014). The prevalence of depression and anxiety disorders in patients with euthyroid Hashimoto's thyroiditis: a comparative study. *General Hospital Psychiatry* **36**, 95–98.

Glaser R, Kiecolt-Glaser JK (2005). Stress-induced immune dysfunction: implications for health. *Nature Reviews: Immunology* **5**, 243–251.

Gold SM, Irwin MR (2009). Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. *Immunology and Allergy Clinics of North America* **29**, 309–320.

Inal V, Kitapcioglu G, Karabulut G, Keser G, Kabasakal Y (2010). Evaluation of quality of life in relation to anxiety and depression in primary Sjogren's syndrome. *Modern Rheumatology* **20**, 588–597.

Irwin MR, Cole SW (2011). Reciprocal regulation of the neural and innate immune systems. *Nature Reviews: Immunology* **11**, 625–632.

Irwin MR, Miller AH (2007). Depressive disorders and immunity: 20 years of progress and discovery. *Brain, Behavior, and Immunity* **21**, 374–383.

Kiecolt-Glaser JK, Glaser R (2002). Depression and immune function: central pathways to morbidity and mortality. *Journal of Psychosomatic Research* **53**, 873–876.

Kirim S, Keskek SO, Koksal F, Haydardedeoglu FE, Bozkirli E, Toledano Y (2012). Depression in patients with euthyroid chronic autoimmune thyroiditis. *Endocrine Journal* **59**, 705–708.

Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, Krogh J (2014). Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* **71**, 1381–1391.

Korczak DJ, Pereira S, Koulajian K, Matejcek A, Giacca A (2011). Type 1 diabetes mellitus and major depressive disorder: evidence for a biological link. *Diabetologia* **54**, 2483–2493.

Kudielka BM, Buske-Kirschbaum A, Hellhammer DH, Kirschbaum C (2004). HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. *Psychoneuroendocrinology* **29**, 83–98.

Lundberg AS, Okkels N, Gustafsson LN, Larsen JT, Sørensen LU, Munk-Jørgensen P (2013). A nationwide study on delirium in psychiatric patients from 1995 to 2011. *Acta Neuropsychiatrica* **26**, 234–239.

Marcus SC, Olfson M (2010). National trends in the treatment for depression from 1998 to 2007. *Archives of General Psychiatry* **67**, 1265–1273.

Matcham F, Rayner L, Steer S, Hotopf M (2013). The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology* **52**, 2136–2148.

Maunder RG, Levenstein S (2008). The role of stress in the development and clinical course of inflammatory bowel disease: epidemiological evidence. *Current Molecular Medicine* **8**, 247–252.

McEwen BS (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological Reviews* **87**, 873–904.

Miller AH, Maletic V, Raison CL (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological Psychiatry* **65**, 732–741.

Miller FW, Alfredsson L, Costenbader KH, Kamen DL, Nelson LM, Norris JM, De Roos AJ (2012). Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. *Journal of Autoimmunity* **39**, 259–271.

Mitsonis CI, Potagas C, Zervas I, Sfagos K (2009). The effects of stressful life events on the course of multiple sclerosis: a review. *International Journal of Neuroscience* **119**, 315–335.

Mors O, Perto GP, Mortensen PB (2011). The Danish Psychiatric Central Research Register. *Scandanavian Journal of Public Health* **39**, 54–57.

Munk-Jorgensen P, Mortensen PB (1997). The Danish Psychiatric Central Register. *Danish Medical Bulletin* **44**, 82–84.

Munk-Jørgensen P, Okkels N, Golberg D, Ruggeri M, Thornicroft G (2014). Fifty years' development and future perspectives of psychiatric register research. *Acta Psychiatrica Scandinavica* **130**, 87–98.

Munk-Jorgensen P, Ostergaard SD (2011). Register-based studies of mental disorders. *Scandanavian Journal of Public Health* **39**, 170–174.

Nery FG, Borba EF, Hatch JP, Soares JC, Bonfa E, Neto FL (2007). Major depressive disorder and disease activity in systemic lupus erythematosus. *Comprehensive Psychiatry* **48**, 14–19.

Nguyen-Nielsen M, Svensson E, Vogel I, Ehrenstein V, Sunde L (2013). Existing data sources for clinical epidemiology: Danish registries for studies of medical genetic diseases. *Clinical Epidemiology* **5**, 249–262.

Pace T, Mletzko T, Alagbe O, Musselman D, Nemeroff C, Miller A, Heim C (2006). Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *American Journal of Psychiatry* **163**, 1630–1633.

Palagini L, Mosca M, Tani C, Gemignani A, Mauri M, Bombardieri S (2013). Depression and systemic lupus erythematosus: a systematic review. *Lupus* **22**, 409–416.

Parker G (2005). Register now: validity later. *Acta Psychiatrica Scandinavica* **112**, 407–418.

Pedersen CB, Gotzsche H, Moller JO, Mortensen PB (2006). The Danish Civil Registration System. A cohort of eight million persons. *Danish Medical Bulletin* **53**, 441–449.

Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, Mortensen PB, Eaton WW (2014). A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry* **71**, 573–581.

Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N (2013). Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Medicine* **11**, 129.

Pop VJ, Maartens LH, Leusink G, van Son MJ, Knottnerus AA, Ward AM, Metcalfe R, Weetman AP (1998). Are autoimmune thyroid dysfunction and depression related? *Journal of Clinical Endocrinology and Metabolism* **83**, 3194–3197.

Raevuori A, Haukka J, Vaarala O, Suvisaari JM, Gissler M, Grainger M, Linna MS, Suokas JT (2014). The increased risk for autoimmune diseases in patients with eating disorders. *PloS ONE* **9**, e104845.

Raison CL, Miller AH (2012). The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). *Molecular Psychiatry* **18**, 15–37.

Rotella F, Mannucci E (2013). Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. *Journal of Clinical Psychiatry* **74**, 31–37.

Roy T, Lloyd CE (2012). Epidemiology of depression and diabetes: a systematic review. *Journal of Affective Disorders* **142**(Suppl), S8–S21.

Schramm C, Wahl I, Weiler-Normann C, Voigt K, Wiegard C, Glaubke C, Brahler E, Lowe B, Lohse AW, Rose M (2014). Health-related quality of life, depression, and anxiety in patients with autoimmune hepatitis. *Journal of Hepatology* **60**, 618–624.

Sharma TR, Kline DB, Shreeve DF, Hartman DW (2011). Psychiatric comorbidities in patients with celiac disease: is there any concrete biological association? *Asian Journal of Psychiatry* **4**, 150–151.

Smith DF, Gerdes LU (2012). Meta-analysis on anxiety and depression in adult celiac disease. *Acta Psychiatrica Scandinavica* **125**, 189–193.

StataCorp (2013). *Stata Statistical Software: Release 13*. StataCorp LP: College Station, TX.

Valtysdottir ST, Gudbjornsson B, Lindqvist U, Hallgren R, Hetta J (2000). Anxiety and depression in patients with primary Sjogren's syndrome. *Journal of Rheumatology* **27**, 165–169.

van de Ven AC, Muntjewerff JW, Netea-Maier RT, de Vegt F, Ross HA, Sweep FC, Kiemeney LA, Vos PE, Buitelaar JK, Hermus AR, den Heijer M, Janzing JG (2012). Association between thyroid function, thyroid autoimmunity, and state and trait factors of depression. *Acta Psychiatrica Scandinavica* **126**, 377–384.

van der Heide F, Wassenaar M, van der Linde K, Spoelstra P, Kleibeuker JH, Dijkstra G (2011). Effects of active and passive smoking on Crohn's disease and ulcerative colitis in a cohort from a regional hospital. *European Journal of Gastroenterology and Hepatology* **23**, 255–261.

van Gool CH, Kempen GI, Bosma H, van Boxtel MP, Jolles J, van Eijk JT (2007). Associations between lifestyle and depressed mood: longitudinal results from the Maastricht Aging Study. *American Journal of Public Health* **97**, 887–894.

Vattakatuchery JJ, Rickards H, Cavanna AE (2011). Pathogenic mechanisms of depression in multiple sclerosis. *Journal of Neuropsychiatry and Clinical Neurosciences* **23**, 261–276.

Voinov B, Richie WD, Bailey RK (2013). Depression and chronic diseases: it is time for a synergistic mental health and primary care approach. *The Primary Care Companion for CNS Disorders* **15**, PCC.12r01468.

Zyrianova Y, Kelly BD, Gallagher C, McCarthy C, Molloy MG, Sheehan J, Dinan TG (2006). Depression and anxiety in rheumatoid arthritis: the role of perceived social support. *Irish Journal of Medical Science* **175**, 32–36.