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Depression and the risk of severe infections: prospective analyses on a nationwide representative sample

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Abstract

Background: Preliminary research suggests an association between depression and subsequent increased risk of infections, yet little is known on this topic. This study investigated the association between depression and risk of various types of infections, including temporal and dose-response relationships.

Methods: A prospective population-based study including 976 398 individuals, of whom 142 169 had a history of depression between 1995 and 2012, was conducted using linked Danish registries. Survival analyses were used to estimate the relative risk of infections among those with depression, compared with those without depression, while adjusting for gender and age.

Results: Depression was associated with increased risk of a wide range of infections [incidence rate ratio (IRR) = 1.61, 95% confidence interval (CI) = 1.49–1.74, $P = 0.000$, for any infection]. There was no evidence of a specific temporal effect but rather a general increased risk of infection subsequent to the onset of depression, as the risk during first year (IRR = 1.67, 95% CI = 1.25–2.22, $P = 0.000$) remained elevated for the ensuing 11 years and beyond (IRR = 1.61, 95% CI = 1.39–1.85, $P = 0.000$). Dose-response analyses revealed that the risk of infection increased by 59% (IRR = 1.59, 95% CI = 1.45–1.75, $P = 0.000$) following a single depressive episode and was elevated even further (IRR = 1.97, 95% CI = 0.92–4.22, $P = 0.082$) following four or more depressive episodes. However, results did not indicate a perfect linear association.

Conclusions: Findings suggest the presence of depression may confer an increased risk of infection and that this increased susceptibility is not confined to a specific time period following the onset of depression. A dose-response relationship may be present, but more research is needed to further examine and confirm a link between depression and risk of infection.

Key words: Depression, infection, humans, prospective studies, population-based, registers

Key Messages

- Depression was associated with increased risk of a wide range of infections.
- Results suggested the increased risk of infection was not confined to a specific time period following the onset of depression.
- More research is needed to further examine the link between depression and risk of infection as well as the dose-response relationship.

Introduction

By 2030, the World Health Organization projects that depression will be the leading contributor to the global disease burden.[1,2] One in five adults experiences depression during their lifetime and substantial personal, social and economic consequences are attributable to depression on both individual and societal levels, with women having a 2-fold increase in risk.[3] Current literature suggests that depression may have a profound and pervasive impact on physical health.[4,5] Previous studies have found that depression is associated with an increased risk of the onset and progression of chronic diseases, such as autoimmune and cardiovascular disorders, as well as potentially increased risk of acute conditions such as infections.[4,6]

Infection remains a major global public health problem, accounting for a quarter to a third of all deaths worldwide, and the annual US infectious disease-related death rate is about 170 000.[7–9] Both microbial and environmental factors (e.g. antimicrobial drug resistance, emergence and re-emergence of infectious agents, globalization, climate change and others) contribute to this problem. There are some clinical data to suggest that depression may be associated with increased risk of infection.[10–12] For instance, one systematic review found that higher levels of depression are associated with an increased susceptibility to unfavourable acute respiratory tract infection outcomes.[13] A large retrospective study with secondary analysis of cross-sectional data on close to 50 000 US college students reported that depression was associated with increased odds of bronchitis, ear infection, sinus infection and streptococcal throat infection.[6] In addition, Irwin and colleagues found that older adults with depression may be at increased risk for herpes zoster (i.e. shingles) compared with sex-matched controls with no history of depression.[10,14] Moreover, depression has also been shown to predict the rate of immune system decay in HIV patients and to prolong and increase levels of pro-inflammatory cytokines subsequent to influenza vaccination, as well as to increase the risk of post-coronary artery bypass grafting infections.[15–17]

Previous studies have had various methodological shortcomings, including: (i) the use of cross-sectional data, which precludes the examination of a temporal relationship between depression and risk of infections; (ii) the inclusion of small sample sizes which obviate the investigation of specific infectious diseases, particularly those that are rare; (iii) the use of selected samples which are not representative of the community; and (iv) the assessment of physical conditions and/or psychological states via self-report, which is subject to misreporting and questionable validity.

The present study sought to investigate the association between depression and the risk of infection using a prospective design in a nationally representative sample of Denmark. Specifically, the study aimed: to investigate the relationship between depression and the risk of specific types of infections, including viral and bacterial infections; to examine the temporal relationship between onset of depression and risk of infections; and to investigate whether there is evidence of a dose-response relationship between the number of depressive episodes and risk of infections.

Method

Study population

In this prospective nationwide register-based study, the cohort was selected through the linkage of several Danish

registries that cover the entire population (currently 5.6 million people). Each individual's general personal information (such as age, gender and history of municipalities of residency) and full treatment history, including all inpatient, outpatient and emergency contacts as well as somatic and psychiatric diagnoses ever received, was linked across the Danish Civil Registration System, the Danish National Hospital Register and the Danish Psychiatric Central Research Register.[18–23] International Classification of Diseases 10 (ICD-10) was introduced in 1994, thus the current study period relied only on data from 1995 and onward, to ensure that consistent diagnostic criteria were employed over time.[24]

Measures

Depressive episode

All diagnoses were documented by physicians during clinical contact in psychiatric treatment settings. In the current study, depression was defined as the presence of a primary diagnosis of depression (ICD-10: F32-F33) in the medical record from 1995 to 2012.[25] A 'primary diagnosis' indicates that the diagnosis was the primary cause of treatment contact, as determined by the treating physician. Individuals with an auxiliary/secondary diagnosis of depression were excluded from the study population. The onset of depression was defined as the date of clinical contact in which a diagnosis of depression was first documented (identified through the Danish Psychiatric Central Research Register). The register includes data on both start and end dates of inpatient, outpatient and emergency contact (outpatient and emergency contacts were incorporated in the register in 1995). Using these data, we aimed to identify a measure of depressive burden, which we defined as the number of depressive episodes. A depressive episode was considered remitted if there was no clinical contact for 6 months or more, including no inpatient or outpatient visits. Clinical contact, following any period of time after the 6 consecutive months of no contact, was then counted as a separate depressive episode. Thus, the number of depressive episodes throughout the study period was calculated as an estimate of depression chronicity.

Infections

First-time clinical contacts due to infection were documented in the Danish National Hospital Register, including inpatient, outpatient and emergency contact. The following infections (using their respective ICD-10 codes) were included and registered:[26] central nervous system (CNS) infections (G03, A17, G00-G01, G04.2, G05.0, A80-A81, A85-A89, B00.3-B00.4, B01.0-B01.1, B02.0-B02.2, B05.0-B05.1, B06.0, B26.1-B26.2, G02.0, G05.1), gastrointestinal infections (A00-A05, A08), liver (ICD-10: B15-B19), respiratory infections (J01-J06, J16-J18, J20.8-J20.9, J21.8-J21.9, J22, A15-A16, A36-A38, J13-J15, J20.0-J20.2, J00, J09-J12, J20.3-J20.7, J21.0-J21.1), sepsis infections (A40-A41), skin infections (L04, A46, L00-L03, L05-L08, B00-B09), urogenital infections (N71-N72, N30.0, N39.0, N41.0-N41.1) and other infections (non-specific group) (A18-A19, A31-A32, A39, A42-A44, A48-A49, B95, B96, B98, H62.0, H67.0, M00, M01.0-M01.3, N61, B25-B34, B97, H62.1, H67.1, M01.4-M01.5). Diagnoses were categorized into either bacterial or viral infection subgroups (the specific grouping of the diagnoses are listed in Supplementary Table S1, available as Supplementary data at *IJE* online).

Procedures

Collectively, the study population consisted of 976 398 individuals. We identified 142 160 individuals with a primary diagnosis of depression and each cohort member was match-controlled with six other individuals with no history of depression on gender, age (i.e. within 6 months of date of birth) and latest municipality of residence (through the Danish Civil Registration System) as a proxy for socioeconomic level. Depressed individuals and matched comparisons were excluded if they, at any time (i.e. both before and during the study period), had a suspected immunosuppression, defined as a diagnosis of malignant neoplasm [ICD8: 140–209, ICD10: C00-C97] and/or AIDS/HIV [ICD8: 07983, ICD-10: B20-B24]. Cohort members and their match-controlled counterparts were followed from the cohort members' first-time clinical contact due to a depressive disorder (earliest start date was the 1 January 1995). Infections were subsequently recorded and individuals were followed until the end of the study period (11 October 2013) but censored in case of death. In case of death of: (i) an individual in the depressed cohort, his/her matched-controls were censored from the date of death and onward; (ii) a matched-controlled individual, the respective depressed individual was allowed to continue in the population at risk as long as he/she still had at least three matched-control individuals who were still being followed.

Statistical analyses

Infection diagnoses were grouped in accordance with the ICD-10 taxonomy as described above. The risk of the specific types of infection was analysed via comparing incidence rates of infection among individuals with a diagnosis of depression with that among their matched counterparts with no such history. All diagnoses of infections were

grouped into an 'any infection' variable and used for the temporal and dose-response analyses. In the temporality analyses, we identified the number of years that preceded the diagnosis of infection subsequent to the onset of the first depressive episode and/or following the date on which the non-depressed matched individuals were first traced. The number of cases of infections for each year as well as incidence rates were then calculated to examine for a potential window of vulnerability to infections following onset of depression. For the dose-response analysis, we identified the number of depressive episodes each individual had experienced. We calculated the incidence rates of infections in relation to the number of depressive episodes. We calculated incidence rate ratios (IRR) and 95% confidence intervals (CI) with stratified Cox regression using STATA13, and chose a significance level at alpha = 0.05. Data were stratified by age and gender in the adjusted analyses. The multiple failure-time survival analysis method described by Andersen and Gill was used due to the possibility of multiple events of infections.[27] This statistical approach allowed individuals to acquire multiple infections including a recurrence of the same type of infection. Individuals could have more than one infection diagnosis simultaneously.

Results

Descriptive measures

This study included 976 398 individuals followed up to a total of 7 760 764 million person-years from 1995 to 2013. The mean age of all individuals upon study entry was 46.3 years [standard deviation (SD) = 20.8 years), the majority of whom were female (63.8%) (shown in Table 1). Out of the 142 169 individuals with depression, 118 112 (83%) experienced one depressive episode, 18 358 (13%) experienced two, 4258 (3%) experienced three and 1441 (1%) experienced four or more. We identified 4570 cases with a diagnosis of infection during the study period, 58% of whom were female. The four most frequent infections (covering 86.4% of all diagnosed infections) were hepatitis (1407; 30.3%), respiratory (914; 19.7%), skin (914; 19.7%) and urogenital infections (775; 16.7%).

Table 1. Age, gender and depression distributions of the study population

	Depression	Comparisons	Total	
Gender	*n*	*n*	*n*	%
Female	90 781	532 410	623 191	63.85
Male	51 388	301 819	353 207	36.15
Total	142 169	834 229	976 398	100.00
Age, years				
Mean	46.5	46.5	46.5	
SD	20.8	20.8	20.8	
Number of depressive episodes	*n*	%	Cumulative %	
1	118 112	83.08	83.08	
2	18 358	12.91	95.99	
3	4258	3.00	98.99	
≥4	1441	1.01	100.00	
Total	142 169	100.00		

Association between depression and risk of different types of infection

Onset of depression predicted an overall subsequent increased risk of infection (IRR = 1.61; CI = 1.49–1.74; $P = 0.000$; adjusted model displayed in Table 2 and Supplementary Figure S1, available as Supplementary data at *IJE* online). Depression was associated with all types of infections that had a sufficient number of cases—sepsis infection had the highest risk (IRR = 2.39; CI = 1.58–3.61; $P = 0.000$) and skin infection had the lowest positive association to depression (IRR = 1.46; CI = 1.17–1.82; $P = 0.001$). CNS and gastrointestinal infections had few cases in the depressed cohort, leaving ambiguous results. We did not find any substantial differences in the magnitude of the association between depression and subsequent bacterial versus viral infections (IRR = 1.70; CI = 1.50–1.92; $P = 0.000$ and IRR = 1.61; CI = 1.44–1.81; $P = 0.000$, respectively, in adjusted model).

Time-related risk of infection following depression onset

Time-related analysis suggested a general increased risk of infection following the onset of depression (see Table 3). During the first year after depression onset, the risk of infection was increased (IRR = 1.67; CI = 1.25–2.22; $P = 0.000$) and did not substantially differ in following years (IRR = 1.61; CI = 1.39–1.85; $P = 0.000$ at 11 years or more later). Overall, results from time-related analysis indicated that the elevated risk of infection following the onset of depression was not restricted to a specific time period (e.g. during the first 2 years after the onset of depression).

Cumulative influences of depressive episodes on risk of infection and gender differences

One, two, three and four or more depressive episodes were all associated with an increased risk of infections, although only one and two depressive episodes yielded *P*-values

Table 2. Incidence rate ratios on the risk of infections following onset of depression

	Comparisons		Depression									
					Crude				Adjusted[a]			
Infection type	Cases	Ir[b]	Cases	Ir[b]	IRR[c]	CI (95%)		*P*	IRR[c]	CI (95%)		*P*
Any infection[d]	3645	54.7	924	84.4	**1.57**	1.44	1.71	0.000	**1.61**	1.49	1.74	0.000
CNS infection	68	1.0	11	1.0	1.00	0.50	2.00	0.994	0.91	0.47	1.73	0.766
Gastrointestinal infection	91	1.4	17	1.6	1.16	0.68	1.97	0.584	1.19	0.71	1.99	0.507
Hepatitis infection	1093	16.4	314	28.7	**1.78**	1.55	2.04	0.000	**1.77**	1.57	2.00	0.000
Respiratory infection	737	11.1	177	16.2	**1.49**	1.26	1.76	0.000	**1.58**	1.36	1.85	0.000
Sepsis infection	77	1.2	25	2.3	**2.01**	1.27	3.21	0.003	**2.39**	1.58	3.61	0.000
Skin infection	744	11.2	170	15.5	**1.42**	1.11	1.81	0.006	**1.46**	1.17	1.82	0.001
Urogenital infection	616	10.0	159	14.5	**1.60**	1.29	1.98	0.000	**1.71**	1.41	2.09	0.000
Other type of infection	266	4.0	72	6.6	**1.68**	1.29	2.19	0.000	**1.72**	1.35	2.19	0.000
Bacterial	1617	242.6	419	38.3	**1.61**	1.40	1.85	0.000	**1.70**	1.50	1.92	0.000
Viral	1441	216.2	379	34.6	**1.63**	1.44	1.85	0.000	**1.61**	1.44	1.81	0.000

[a]Adjusted for gender and age.
[b]Incidence rates per 100 000 person-years.
[c]Boldface is $P < 0.05$ and underslash is $< P = 0.01$.
[d]All types of infection.

Table 3. Incidence rate ratios of any infection since the time of onset of depression

Time since onset of first depression (years) and since start date of tracing for comparisons	Comparisons		Depression					
	Cases	Ir[a]	Cases	Ir[a]	IRR[b]	CI (95%)		*P*
< 1	220	1131.5	64	1891.9	**1.67**	1.25	2.22	0.000
1	268	258.6	64	352.2	**1.36**	1.02	1.79	0.031
2	295	179.4	86	292.0	**1.63**	1.26	2.08	0.000
3	270	118.1	61	150.0	1.27	0.95	1.68	0.098
4	231	83.4	57	115.2	**1.38**	1.02	1.85	0.034
5 to 10	1375	59.3	345	86.1	**1.45**	1.29	1.63	0.000
≥ 11	986	27.7	247	44.6	**1.61**	1.39	1.85	0.000

[a]Incidence rates per 100 000 person-years.
[b]Boldface is $P < 0.05$ and underslash is $P < 0.01$.

Table 4. Cumulative effect of depressive episodes on the risk of infections[a]

Number of depressive episodes			Crude				Adjusted[a]			
	Cases	Ir[b]	IRR[c]	CI (95%)		*P*	IRR[c]	CI (95%)		*P*
1	781	83.2	**1.59**	1.45	1.75	0.000	**1.64**	1.51	1.79	0.000
2	107	88.3	**1.47**	1.17	1.83	0.001	**1.49**	1.21	1.83	0.000
3	24	103.2	1.31	0.81	2.12	0.274	1.25	0.80	1.97	0.325
≥ 4	9	134.3	1.97	0.92	4.22	0.082	1.84	0.95	3.59	0.072

[a]Adjusted for gender and age.
[b]Incidence rates per 100 000 person-years.
[c]Boldface is $P < 0.05$ and underslash is $P < 0.01$.

below 0.05 (see Table 4 and Supplementary Figure S2, available as Supplementary data at *IJE* online). Overall, the incidence rates of infections increased with the number of depressive episodes, and the risk of infections changed from IRR = 1.59 (CI = 1.45–1.75; $P = 0.000$) at one depressive episode to an increased risk of IRR = 1.97 (CI = 0.92–4.22; $P = 0.082$) at four or more depressive episodes in the crude model (the adjusted model had IRR = 1.64; CI = 1.51–1.79; $P = 0.000$ at one depressive episode and IRR = 1.84; CI = 0.95–3.59; $P = 0.072$ at four

or more depressive episodes). Dose-response analysis did not show any substantial differences in the magnitude of association between depression and risk of bacterial versus viral infections (data not shown). A single depressive episode was associated with an increased risk of infection for both males and females (IRR = 1.55; CI = 1.32–1.81; $P = 0.000$ and IRR = 1.64; CI = 1.46–1.84; $P = 0.000$, respectively) (see Table 5). The risk of infection associated with recurrent depression was not elevated, relative to a single episode, and only the association among females remained increased with an IRR of 1.61 (CI = 1.26–2.05; $P = 0.000$) (and IRR = 1.23; CI = 0.89–1.71; $P = 0.202$ for males).

Discussion

This study has three main findings. First, a history of depression appears to be associated with an increased risk of a wide range of infections, compared with no history of depression. Second, the increased risk of infections following the onset of depression remained relatively consistent over time. Third, there is some evidence of a dose-response relationship between the number of depressive episodes and the risk of infections, but results did not suggest a strong and perfectly linear association. These findings collectively suggest that increased vulnerability to infection may be an additional health risk associated with depression.

From observational data such as these, inferences about causality cannot be made. However, there is a hypothesis suggesting a biological bidirectional relationship may exist. Specifically, the association between depression and risk of infections may be mediated through depression-induced immunological changes. By triggering neuroendocrine stress-signalling pathways (such as the sympathetic nervous system and hypothalamic-pituitary-adrenal axis), which regulate multiple internal physiological processes including broad patterns of transcriptional activity in cells of the immune system, depression may potentially affect the steering of immunological gene expression.[28] Depression has prolonged stimulatory effects on these neuro-immunological connections and their chronic activation can alter immune system function and thereby contribute to an increased susceptibility to infectious agents.[5,28–31] Previous literature suggests a bidirectional association between depression and inflammation. Several potential molecular signalling pathways have been suggested for pro-inflammatory cytokines and antiviral signals to modulate the activity of behavior-related neurotransmitters such as dopamine, serotonin and noradrenalin.[28,29] Therefore, it is also likely that occurrence of infections could induce depression.[29,32] This is further supported by epidemiological studies that have linked increased cytokines levels with risk of depression and a recent meta-analysis that suggested anti-inflammatory treatment to decrease depressive symptoms.[33–35] In addition, recent register-based studies suggest that infections in combination with autoimmune diseases increase the risk of mood disorders and schizophrenia.[26,36] Our time analyses support the notion that the herein presented findings address the risk of infection due to the onset of depression. Due to the choice of study design, namely a prospective cohort from 1995 and onward, infections before the study period were not captured or accounted for. However, given the bidirectional interplay between depression and the immune system, future prospective studies are needed to describe the reverse relationship between infection and the risk of depression.

Our results did not suggest a specific window of time in which the risk of infections was highest following the onset of depression. There could be a number of explanations for this finding. First, the time of diagnosis (and thus its appearance in the registers) of both depression and infections are not necessarily tightly aligned with the actual onset of the diseases. Second, the allostatic load of depression burden that causes an enhanced susceptibility to infections may differ across individuals in the population.[37] In addition, the course and magnitude of depression may interpersonally differ in the study population. Importantly, the consistency in increased risk of infections over time after the onset of depression could indicate that the found association of increased risk of infection does not stem from Berkson's fallacy (i.e. biased by the clinical contact due to depression) and thus heighten the possibility of causality. In addition, a potential distinct time period of increased risk cannot be rejected from these results. For example, an acute increased risk of infection following the onset of depression could still exist. However, given the potential delay from the actual onset of depression to the time of diagnosis, a register data-based study such as this may not

Table 5. Incidence rate ratios for infections in relation to single depressive episode and recurrent depression when divided into genders[a]

		Any infections					
Female		**Cases**	**Ir[b]**	**IRR[c]**	**CI (95%)**		***P***
Depressive Episode:	1	454	75.1	**1.64**	1.46	1.84	0.000
	≥ 2	92	86.9	**1.61**	1.26	2.05	0.000
Male							
Depressive episode:	1	327	97.7	**1.55**	1.32	1.81	0.000
	≥ 2	48	103.5	1.23	0.89	1.71	0.202

[a]Adjusted for age.
[b]Incidence rates per 100 000 person-years
[c]Boldface is $P < 0.05$ and underslash is $P < 0.01$.

adequately capture that information. Thus, future research that can incorporate more sensitive measures of time is needed.

Our findings indicated an increased relative risk of infections of 64% (IRR = 1.64; CI 1.51–1.79; $P = 0.000$) with one depressive episode and up to 84% (IRR = 1.84; CI = 0.95–3.59; $P = 0.072$) with four or more depressive episodes (in the adjusted model). However, results from three and four or more depressive episodes should be interpreted cautiously due to the very low number of cases. In addition, a dose-response relationship was not perfectly trended (see Table 4). First, this could be because our method of depression assessment may have failed to perfectly capture the accumulation of depressive burden using the number of episodes defined in this way. Second, it is possible that depressive episodes occurred before the study period for the individuals in the depression-exposed group (i.e. the matched-control group had no history of depression either before or during the study period), which would not have been accounted for in the assessment of depression burden. Third, it is possible that the risk of some types of infection may follow a dose-response relationship whereas others do not, and the grouping of all infections together could have obscured this finding. Fourth, very few depressed individuals had more than two depressive episodes. Therefore, results of the dose-response analysis should be interpreted with caution due to small cell size.

Study results need to be considered in light of key limitations. First, general limitations to registry research include the heterogeneity and questionable validity of the clinical data collected.[25,38,39] Therefore, we did not find it suitable to differentiate between different subtypes of depression and thus the study did not sufficiently assess the severity of depression. However, as the depressive episodes have led individuals to psychiatric treatment care (as opposed to those not seeking help, or getting treatment via general practitioners in primary care services), their depressive symptoms were less likely to be mild. With respect to the definition of depressive episode, it is also possible that current treatment might prevent recurrent depression via the ongoing use of antidepressant medications. Ongoing treatment may lead to continued clinical contact despite complete resolution of the index depressive episode, and would be more likely among individuals who either had more severe depression, or who had had at least one recurrence of depressive disorder after the initial episode. This may potentially be a challenge that other registry-based studies could address.

Second, mental health data captured in the Danish registries are based on diagnoses given in psychiatric treatment settings, which likely leads to an underreporting of depression.[25] Therefore, despite the nationwide population-based design of this study, we cannot rule out the possibility of selection bias. Thus our results are likely conservative estimates, as some individuals within the comparison group may have had unreported depressive symptoms, which could subsequently contribute to the infection rate within this group.

Third, low socioeconomic status (SES) is independently associated with both depression and the risk of infections.[40,41] The dataset used to conduct these analyses did not allow for adjusting for any potential confounding of various SES factors such as income level, relationship status, education level and occupation. The absence of such information/adjustment has also been documented in similar recent Danish register studies.[26,42] Toward controlling for SES differences with the information we do have, our study matched the assessed population on municipality of residency as an approximate method for controlling for potential SES confounding. Area of residency adjustments have previously been shown to be a powerful method for controlling for SES-related differences in both mental and somatic illnesses, including rates of both depression and infections, and thus any potential confounding with depression via those associations.[40,43–48] Furthermore, a recent Danish register study on 30-day mortality after infection among persons with either schizophrenia or bipolar disorder reported no differences in results after performing sensitivity analyses on SES (i.e. in this case education level).[49] Still, we cannot reject SES as being an alternative explanation for the herein shown link between depression and the risk of infection,[4] and these findings should be replicated with datasets that can control fully for SES.

Last, we were unable to adjust for various potential confounding factors (e.g. environmental factors, cigarette smoking, obesity, comorbidity of physical conditions)[50] as the registries do not obtain sufficient data. Thus, this uncontrolled confounding could bias the result. However, previous studies have adjusted for these covariates when assessing the association between depression and other somatic conditions and have reported a vaguely lower effect size.[4] Nonetheless, these factors could still partly influence the herein reported findings and future studies that assess the association between depression and risk of infection in the co-occurrence of other physical conditions would be essential in strengthening the argument for potential causality.[4]

The study has a number of strengths. This study was representative of the entire Danish population and included all individuals with a primary diagnosis of depression given in psychiatric treatment settings from 1995 through 2012. Using this approach, we had a unique opportunity to conduct large prospective analyses on the association between depression and the risk of a wide range

of infections in an epidemiological sample reflective of the population.[20] Moreover, our study design minimized the risk of selection and recall biases, as depression and infection diagnoses were collected prospectively through clinical records, and all public hospital treatment in Denmark is free of charge. Our results suggest that the link between depression and infection risk extends quite broadly beyond specific subgroups and types of infection.

In sum, the present findings indicate an association between depression and an increased risk of the development of several types of infection. Findings did not suggest that the increased risk of infection was confined to a limited time period following the onset of depression, as the risk of infection remained increased throughout the study period. Although the results did not fully support a dose-response correlation, it may still exist. Collectively, these findings highlight the influence of depression on health, suggesting additional clinical implications in the treatment and management of depression.

Supplementary Data

Supplementary data are available at *IJE* online.

Author contributions

P.M-J., and N.W.A. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. N.W.A., N.O., P.M-J., S.W.C. and R.D.G. developed the aims of the study; N.W.A., N.O. and P.M-J. obtained study data; N.W.A., P.M-J. and L.G. conducted statistical analyses; N.W.A., L.G., S.W.C. and R.D.G. interpreted the results; N.W.A. drafted the manuscript with assistance and critical feedback from N.O., R.D.G., P.M-J., S.W.C., and F.T.

Conflict of interest: The authors have no conflicts of interest to declare.

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