It is illegal to post this copyrighted PDF on any website.

Leptospirosis and Depression: A Nationwide Cohort Analysis

Chun-Hsiang Chiu, MD[a,b]; Ying-Chuan Wang, MD[c]; Cheng-Li Lin, MSc[d,e]; Feng-You Lee, MD[f]; and Chia-Hung Kao, MD[g,h,i,*]

ABSTRACT

Objective: We conducted a retrospective cohort study to investigate whether leptospirosis is a risk factor for depression.

Method: From the Taiwan National Health Insurance Research Database between 2000 and 2010, patients with leptospirosis (*ICD-9* code 100) who did not have a history of depression (*ICD-9-CM* codes 296.2, 296.3, 300.4, and 311) before the index date were enrolled (leptospirosis cohort). For each patient with leptospirosis, 1 control without a history of leptospirosis and depression was randomly selected (nonleptospirosis cohort). Cox proportional hazards regression models were used to analyze the risk of depression according to sex, age, and comorbidities.

Results: In the leptospirosis and nonleptospirosis cohorts, we observed 34 patients with depression, with the incidence rate of 2.87 per 1,000 person-years, and 25 patients with depression, with the incidence rate of 1.93 per 1,000 person-years, respectively, yielding a crude hazard ratio (HR) of 1.49 (95% confidence interval [CI], 1.25–1.77) and an adjusted HR (aHR) of 1.58 (95% CI, 1.34–1.88). Compared with the nonleptospirosis cohort, the leptospirosis cohort had a risk of depression stratified by sex, age, and comorbidity that was higher in female patients (aHR = 2.08; 95% CI, 1.54–2.80), patients younger than 49 years old (aHR = 3.19; 95% CI, 2.39–4.27), and patients without comorbidity (aHR = 2.14; 95% CI, 1.68–2.71). The risk of depression was higher in women than in men (aHR = 1.90; 95% CI, 1.61–2.25) and in patients with comorbidities, namely hyperlipidemia (aHR = 1.80; 95% CI, 1.40–2.31), coronary artery disease (aHR = 2.47; 95% CI, 1.96–3.12), stroke (aHR = 1.77; 95% CI, 1.39–2.24), and septicemia (aHR = 2.06; 95% CI, 1.64–2.58).

Conclusions: Patients with leptospirosis have a 1.58-fold higher risk of depression than that in the general population. Physicians should be alert to the emotional condition and depression symptoms of people who had been suffering from leptospirosis.

J Clin Psychiatry 2017;78(4):e398–e403
https://doi.org/10.4088/JCP.16m10773
© Copyright 2017 Physicians Postgraduate Press, Inc.

[a]Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei City, Taiwan
[b]Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei City, Taiwan
[c]Department of Family Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei City, Taiwan
[d]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[e]College of Medicine, China Medical University, Taichung, Taiwan
[f]Department of Emergency Medicine, Taichung Tzu Chi Hospital, Taichung, Taiwan
[g]Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan
[h]Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan
[i]Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan
**Corresponding author:* Chia-Hung Kao, MD, Graduate Institute of Clinical Medicine Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Deh Rd, Taichung 404, Taiwan (d10040@mail.cmuh.org.tw).

Leptospirosis is one of the most common zoonotic infections in the world[1] and mostly occurs in temperate and tropical climates.[2,3] It is usually encountered in developing countries but is also reported in European countries and the United States.[4–6] It is caused by *Leptospira* species, which comprise 24 serogroups and 250 serovars.[2] Pathogenic leptospires colonize the renal tubules of reservoir hosts and are excreted through urine into the environment. People become infected during contact with contaminated soil and water. Thus, leptospirosis is an occupational hazard for people who work outdoors or with animals, such as farmers, sewer workers, veterinarians, dairy farmers, and military personnel.[7,8] The presentation of leptospirosis varies from asymptomatic illness and self-limited febrile illness to severe disease forms such as Weil disease (a triad of jaundice, acute renal failure, and bleeding), chronic interstitial nephritis, meningitis, myocarditis, hemolytic crisis, and multi-organ failure.[9]

Depression is one of the most commonly diagnosed mental disorders among adults, registering a lifetime prevalence rate of 16.6%.[10] According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, depressive disorders include disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition, among others.[11] The common feature of all of these disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. Depression is not a homogeneous disorder but a complex phenomenon having various subtypes, a highly variable course, and no established mechanisms.[11]

Studies evaluating the relationship between infection and depression were rare until Canli[12] suggested that depression has an infectious origin. Studies of inflammatory biomarkers in major depression strongly suggested an inflammatory origin. A meta-analysis of 24 studies[13] confirmed prior reports of tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 levels in patients with major depression. Another meta-analysis of 29 studies[14] reported a significantly elevated soluble IL-2 receptor level. Compared with age-matched controls, patients with major depression had increased levels of transmembrane TNF-α in Brodmann area 46 (BA 46), a region associated with emotion,[15] and differential

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2017 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Clinical Points

- Depression is not a homogeneous disorder but a complex phenomenon having various subtypes, a variable course, and no established mechanisms.
- Infection may be one of the risk factors of depression.
- Depression and leptospirosis may share parts of the underlying pathogenesis. Further studies should be conducted to confirm this epiphenomenon.

expression of a large set of both anti-inflammatory and proinflammatory markers (including IL-1α, IL-2, IL-3, IL-5, IL-8, IL-9, IL-10, IL-12A, IL-13, IL-15, IL-18, and IFN-γ) in BA 10, a region associated with reward processing.[16]

Although leptospirosis was found to be associated with several chronic diseases,[17,18] studies evaluating the relationship between leptospirosis and depression are rare. Thus, we investigated the risk of depression in patients with leptospirosis.

METHODS

Data Source

We enrolled patients from the National Health Insurance Research Database (NHIRD) of Taiwan, which was established by the National Health Research Institutes. The data in the NHIRD are derived from the National Health Insurance (NHI) program, which was implemented in 1995 and provides comprehensive medical coverage to 99% of the Taiwanese population of 23.75 million.[19] The details of the NHI program have been adequately described in previous high-quality articles.[20,21] Patient identification numbers were encrypted before the release of the data for research to ensure patient privacy. Diseases were defined according to the *International Classification of Diseases*, Ninth Revision, Clinical Modification (*ICD-9-CM*) codes. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115). The IRB also specifically waived the consent requirement.

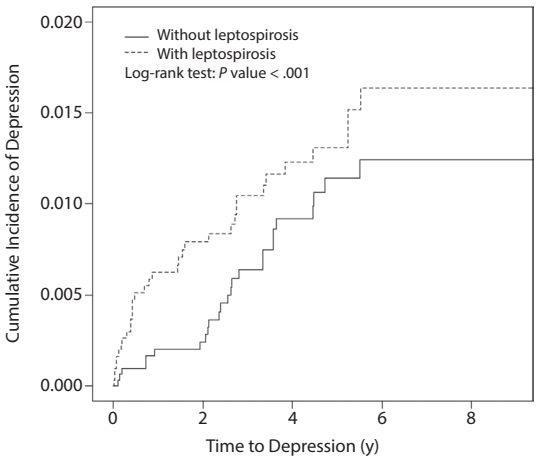
Sampled Patients

We included patients newly diagnosed with leptospirosis (*ICD-9* code 100) between 2000 and 2010 according to inpatient claims. The initial date of hospitalization with a leptospirosis diagnosis was identified as the index date. Patients with a history of depression (*ICD-9-CM* codes 296.2, 296.3, 300.4, and 311), aged <20 years, or having missing data for sex or birth date were excluded. NHI beneficiaries aged ≥20 years and without leptospirosis were randomly included in the nonleptospirosis cohort; they were frequency matched with the patients in the leptospirosis cohort at a 1:1 ratio according to sex; age (5-year span); year of the index date; comorbidities, namely diabetes, hypertension, hyperlipidemia, coronary artery disease (CAD), stroke, and septicemia; and index year. The same exclusion criteria were applied to the nonleptospirosis cohort. Major depressive disorder single episode (*ICD-9-CM* code 296.2), major depressive disorder recurrent episode (*ICD-9-CM* code 296.3), dysthymic disorder convert (*ICD-9-CM* code 300.4), and depressive disorder, not elsewhere classified (*ICD-9-CM* code 311) were defined as the end point of this study. All study patients were followed up until end point occurrence, loss to follow-up, death, withdrawal from insurance, or the end of 2011.

Table 1. Demographic Characteristics and Comorbidity in Patients With and Without Leptospirosis

Variable	Leptospirosis No (n = 3,154)	Leptospirosis Yes (n = 3,154)	*P* Value
Sex, n (%)			.67
Female	1,016 (32.2)	1,000 (31.7)	
Male	2,138 (67.8)	2,154 (68.3)	
Age, mean (SD), y	53.1 (16.8)	52.9 (16.6)	.77
Stratified age, n (%), y			.71
≤49	1,383 (43.8)	1,386 (43.9)	
50–64	914 (29.0)	937 (29.7)	
≥65	857 (27.2)	831 (26.3)	
Comorbidity, n (%)			
Diabetes	558 (17.7)	556 (17.6)	.95
Hypertension	782 (24.8)	778 (24.7)	.91
Hyperlipidemia	222 (7.04)	217 (6.88)	.80
Coronary artery disease	269 (8.53)	270 (8.56)	.96
Stroke	281 (8.91)	286 (9.07)	.83
Septicemia	397 (12.6)	397 (12.6)	.99

Figure 1. Comparison of the Cumulative Incidence of Depression Between Leptospirosis and Nonleptospirosis Cohorts by Using the Kaplan-Meier Method



Comorbidities

Underlying comorbidities, namely diabetes (*ICD-9-CM* code 250), hypertension (*ICD-9-CM* codes 401–405), hyperlipidemia (*ICD-9-CM* code 272), CAD (*ICD-9-CM* codes 410–414), stroke (*ICD-9-CM* codes 430–438), and septicemia (*ICD-9-CM* codes 003.1, 036.2, 038, 790.7), were evaluated.

Statistical Analysis

Student *t* tests and χ^2 tests were used to examine differences in demographic characteristics and comorbidities

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2017 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 2. Incidence and Hazard Ratio (HR) for Depression and Depression-Associated Risk Factor

Variable	Event	Person-years	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)
Leptospirosis					
No	25	12,973	1.93	1.00	1.00
Yes	34	11,829	2.87	1.49 (1.25–1.77)**	1.58 (1.34–1.88)**
Sex					
Female	28	7,893	3.55	1.94 (1.63–2.30)**	1.90 (1.61–2.25)**
Male	31	16,910	1.83	1.00	1.00
Age, y					
≤49	22	11,485	1.92	1.00	1.00
50–64	16	7,351	2.18	1.14 (0.92–1.41)	0.84 (0.67–1.05)
≥65	21	5,966	3.52	1.84 (1.50–2.24)**	1.12 (0.89–1.41)
Comorbidity					
Diabetes					
No	48	20,960	2.29	1.00	1.00
Yes	11	3,843	2.86	1.25 (1.00–1.56)*	0.77 (0.61–1.00)
Hypertension					
No	39	19,397	2.01	1.00	1.00
Yes	20	5,405	3.70	1.84 (1.54–2.20)**	0.98 (0.78–1.22)
Hyperlipidemia					
No	50	23,258	2.15	1.00	1.00
Yes	9	1,544	5.83	2.71 (2.14–3.44)**	1.80 (1.40–2.31)**
Coronary artery disease					
No	46	22,955	2.00	1.00	1.00
Yes	13	1,847	7.04	3.51 (2.86–4.31)**	2.47 (1.96–3.12)**
Stroke					
No	48	22,963	2.09	1.00	1.00
Yes	11	1,839	5.98	2.86 (2.30–3.56)**	1.77 (1.39–2.24)**
Septicemia					
No	47	22,541	2.09	1.00	1.00
Yes	12	2,262	5.31	2.54 (2.06–3.14)**	2.06 (1.64–2.58)**

[a]Incidence rate, per 1,000 person-years.
[b]Crude HR.
[c]Adjusted HR; multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, stroke, and septicemia.
*$P < .05$.
**$P < .001$.

(%) between the leptospirosis and nonleptospirosis cohorts. The cumulative incidence of depression was plotted using the Kaplan-Meier method, and differences were determined using the log-rank test. Incidence density rates (per 1,000 person-years) of depression were estimated according to sex, age, and comorbidities. Univariable and multivariable Cox proportional hazards regressions were used to determine the risk of depression, which was presented as a hazard ratio (HR) with a 95% confidence interval (CI). The multivariable model was simultaneously adjusted for age and the comorbidities, namely diabetes, hypertension, hyperlipidemia, CAD, stroke, and septicemia. All data processing procedures and statistical analyses were performed using the SAS software, Version 9.4 (SAS Institute, Inc, Cary, North Carolina). All *P* values were 2 tailed, and a *P* value of < .05 was considered significant.

RESULTS

The leptospirosis and nonleptospirosis cohorts were well matched according to sex, age, and comorbidities; men were predominant (68.3% men vs 31.7% women in the leptospirosis group), and 43.9% of the patients were ≤ 49 years old (Table 1).

The mean age of patients in the leptospirosis and nonleptospirosis cohorts was 52.9 ± 16.6 and 53.1 ± 16.8 years, respectively. The mean follow-up period in the leptospirosis and nonleptospirosis cohorts was 3.75 and 4.11 years, respectively. The cumulative incidence of depression was higher for the patients in the leptospirosis cohort than for those in the nonleptospirosis cohort (log-rank test $P < .001$, Figure 1).

The overall incidence of depression was higher in the leptospirosis cohort than in the nonleptospirosis cohort (2.87 and 1.93 per 1,000 person-years, respectively; crude HR = 1.49; 95% CI, 1.25–1.77), with an adjusted HR (aHR) of 1.58 (95% CI, 1.34–1.88) after adjustment for age, sex, and comorbidities (Table 2). The mean duration between leptospirosis and subsequent depression was 1.64 years. As for all study subjects, the risk of depression was higher in women than in men (aHR = 1.90; 95% CI, 1.61–2.25). The risk of depression was higher in patients with comorbidities, namely hyperlipidemia (aHR = 1.80; 95% CI, 1.40–2.31), CAD (aHR = 2.47; 95% CI, 1.96–3.12), stroke (aHR = 1.77; 95% CI, 1.39–2.24), and septicemia (aHR = 2.06; 95% CI, 1.64–2.58).

We determined the incidence of depression in both cohorts and observed that the patients in the leptospirosis cohort had a significantly higher risk of depression (Table 3). Moreover, compared with the nonleptospirosis cohort, the risk of depression stratified by sex, age, and comorbidity

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2017 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 3. Comparison of Incidence and Hazard Ratio (HR) of Depression Stratified by Sex, Age, and Comorbidity Between Patients With and Without Leptospirosis

	Without Leptospirosis					With Leptospirosis				
Variable	Event	Person-Years	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)	Event	Person-Years	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)
Sex										
Female	10	4,132	2.42	1(Reference)	1(Reference)	18	3,761	4.79	1.98 (1.46–2.68)*	2.08 (1.54–2.80)*
Male	25	8,841	1.70	1(Reference)	1(Reference)	16	8,069	1.98	1.17 (0.95–1.45)	1.21 (0.98–1.49)
Stratified age, y										
≤49	6	5,972	1.00	1(Reference)	1(Reference)	16	5,512	2.90	2.889 (2.15–3.88)*	3.19 (2.39–4.27)*
50–64	7	3,701	1.89	1(Reference)	1(Reference)	9	3,651	2.47	1.30 (0.95–1.79)	1.35 (0.99–1.82)
≥65	12	3,300	3.64	1(Reference)	1(Reference)	9	2,667	3.38	0.93 (0.67–1.28)	0.92 (0.67–1.27)
Comorbidity[d]										
No	8	8,104	0.99	1(Reference)	1(Reference)	16	7,594	2.11	2.13 (1.67–2.72)*	2.14 (1.68–2.71)*
Yes	17	4,869	3.49	1(Reference)	1(Reference)	18	4,235	4.25	1.22 (0.94–1.58)	1.21 (0.93–1.56)

[a]Incidence rate, per 1,000 person-years.
[b]Crude HR.
[c]Adjusted HR; multivariable analysis including age and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, stroke, and septicemia.
[d]Patients with any one of the comorbidities (diabetes, hypertension, hyperlipidemia, coronary artery disease, stroke, and septicemia) were classified as the comorbidity group.
*$P < .001$.

Table 4. Comparison of Incidence and Hazard Ratio (HR) of Subtype of Depression Between Patients With and Without Leptospirosis

	Without Leptospirosis				With Leptospirosis			
Subtype	Event	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)	Event	Rate[a]	Crude HR[b] (95% CI)	Adjusted HR[c] (95% CI)
Major depressive disorder single episode	3	0.23	1(Reference)	1(Reference)	9	0.76	3.29 (2.64–4.10)*	3.43 (2.77–4.24)*
Major depressive disorder recurrent episode	3	0.23	1(Reference)	1(Reference)	3	0.25	1.10 (0.90–1.34)	1.17 (0.96–1.41)
Dysthymic disorder convert	5	0.39	1(Reference)	1(Reference)	13	1.10	2.85 (2.32–3.51)*	2.95 (2.41–3.60)*
Depressive disorder, not elsewhere classified	18	1.39	1(Reference)	1(Reference)	17	1.44	1.04 (0.87–1.24)	1.10 (0.92–1.31)

[a]Incidence rate, per 1,000 person-years.
[b]Crude HR.
[c]Adjusted HR; multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, stroke, and septicemia.
*$P < .001$.

in the leptospirosis cohort was higher in female patients (aHR = 2.08; 95% CI, 1.54–2.80, $P < .001$), patients younger than 49 years old (aHR = 3.19; 95% CI, 2.39–4.27, $P < .001$), and patients without comorbidity (aHR = 2.14; 95% CI, 1.68–2.71, $P < .001$).

For a more specific diagnosis of depression, when compared with the nonleptospirosis cohort, patients with leptospirosis exhibited a 3.43-fold increased risk of major depressive disorder single episode (95% CI, 2.77–4.24) and exhibited a 2.95-fold increased risk of dysthymic disorder convert (95% CI, 2.41–3.60) (Table 4).

DISCUSSION

Leptospirosis is one of the most common zoonotic infections worldwide.[1] Studies evaluating the relationship between leptospirosis and depression are scant. This is the first study reporting that patients with leptospirosis have a 1.58-fold higher risk of depression than that in the general population.

Depression is one of the most common mental disorders worldwide. Our understanding of the nature of depression has considerably changed in the last 2 decades, from being regarded as an acute and self-limiting illness to currently being increasingly considered as a chronic disease. The main hypotheses regarding the etiology of depression include the monoamine deficiency hypothesis and the hypothalamic-pituitary-adrenal axis hypothesis.[22] Increasing evidence suggests that vascular disease of the brain may also predispose people to depression in late life.[23–32] Three types of studies (clinical, neuroimaging, and neuropathology) have revealed that the prevalence of vascular disease, particularly cerebrovascular disease, is higher in patients with depression.[23–32] Otherwise, Rybakowski[33] et al reported that, compared with controls, patients with depression had impaired arterial endothelial function. Endothelial dysfunction–related vascular disease may be one pathoetiology of depression.

Endothelial dysfunction and systemic inflammation are also involved in the pathogenesis of leptospirosis. Leptospires frequently enter the body through skin abrasions or exposed mucous membranes and spread through the bloodstream and tissues without initial inflammation. Furthermore, an immune phase characterized by antibody production follows. Vasculitis, endothelial damage, and inflammatory infiltrates consisting of monocytic cells, plasma cells, histiocytes, and neutrophils develop in any tissue affected in this phase and lead to clinical symptoms and complications.[9] The endothelial damage and systemic inflammatory processes caused by leptospirosis may be the pathogenic mechanisms

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2017 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

underlying the association of leptospirosis and an increased risk of depression.

In the current study, we observed that the aHR of depression was 1.90-fold higher in women than in men (95% CI, 1.61–2.25). This finding is consistent with that in a previous study.[34] In addition, the risk of depression was higher in patients with comorbidities, namely hyperlipidemia (aHR = 1.80; 95% CI, 1.40–2.31), CAD (aHR = 2.47; 95% CI, 1.96–3.12), stroke (aHR = 1.77; 95% CI, 1.39–2.24), and septicemia (aHR = 2.06; 95% CI, 1.64–2.58). This finding suggests an involvement of these comorbid diseases in the pathogenic mechanisms underlying depression, such as systemic inflammation and endothelium dysfunction.

The incidence of depression in the leptospirosis cohort, compared with the nonleptospirosis cohort, was higher in female patients, patients younger than 49 years, and patients without comorbidities (diabetes, hypertension, hyperlipidemia, CAD, stroke, and septicemia). This finding indicates that leptospirosis might be an independent risk factor for depression. Although septicemia was one of the risk factors of depression, the increase of depression risk in patients with leptospirosis was not attributed to septicemia. Leptospirosis itself may be a risk factor for the development of depression rather than just one of the organisms that cause severe sepsis leading to depression.

We enrolled a large sample of patients in this study because the NHI is universal and mandatory in Taiwan. However, our study has some limitations that must be addressed. First, the diagnosis of leptospirosis was determined using *ICD-9-CM* codes from the NHIRD; however, leptospirosis infection with mild symptom presentation might have been misclassified and coded as flu-like disease, potentially leading to underestimation of the risk of depression. Second, personal information such as education level, occupational history, socioeconomic status, individual behavior (eg, smoking habits and exercise habits), drug history, and family history is not recorded in the NHIRD. These may have been confounding factors in this study. Third, we enrolled patients with leptospirosis who were hospitalized; thus, they may have had relatively severe symptoms. A higher risk of depression may be observed only in patients with leptospirosis who have severe symptoms and require hospitalization.

Our study revealed that patients with leptospirosis have a higher risk of depression than that in the general population. The average duration between leptospirosis and subsequent depression is 1.64 years. Physicians should be alert to the emotional condition and depression symptoms of people who have been suffering from leptospirosis in past years, especially those who had severe symptoms and required hospitalization. Routine screening of depression among these people may have clinical benefits of early detection and treatment of depressive disorders.

In conclusion, this is the first study investigating the relationship between leptospirosis and depression. Patients with leptospirosis have a 1.58-fold higher risk of depression than that in the general population. This finding highlights the role of endothelial dysfunction and systemic inflammation in depression. Additional studies should be conducted in the future to confirm this epiphenomenon.

Submitted: February 26, 2016; accepted July 15, 2016.

Online first: March 14, 2017.

Author contributions: Individual author contributions were as follows: conception and design: Drs Chiu and Kao; administrative support: Dr Kao; collection and assembly of data: all authors; data analysis and interpretation: all authors; manuscript writing: all authors; and final approval of manuscript: all authors.

Potential conflicts of interest: The authors report no conflicts of interest.

Funding/support: This study was supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019); China Medical University Hospital; Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037); NRPB Stroke Clinical Trial Consortium (MOST 104-2325-B-039 -005); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; China Medical University under the Aim for Top University Plan of the Ministry of Education, Taiwan; and Tri-Service General Hospital (TSGHC105-117, TSGHC105-065). No additional external funding was received for this study.

Role of the sponsor: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

1. Levett PN. Leptospirosis. *Clin Microbiol Rev*. 2001;14(2):296–326.
2. Singh SS, Vijayachari P, Sinha A, et al. Clinico-epidemiological study of hospitalized cases of severe leptospirosis. *Indian J Med Res*. 1999;109:94–99.
3. Daher E, Zanetta DM, Cavalcante MB, et al. Risk factors for death and changing patterns in leptospirosis acute renal failure. *Am J Trop Med Hyg*. 1999;61(4):630–634.
4. Holk K, Nielsen SV, Rønne T. Human leptospirosis in Denmark 1970–1996: an epidemiological and clinical study. *Scand J Infect Dis*. 2000;32(5):533–538.
5. Gsell O. The changing epidemiology of leptospirosis in Europe: a report on the 6th meeting of European Leptospira workers, Brnò, Czechoslovakia, September 1988. *Zentralbl Bakteriol*. 1990;273(3):412–427.
6. Katz AR, Ansdell VE, Effler PV, et al. Assessment of the clinical presentation and treatment of 353 cases of laboratory-confirmed leptospirosis in Hawaii, 1974–1998. *Clin Infect Dis*. 2001;33(11):1834–1841.
7. Bharti AR, Nally JE, Ricaldi JN, et al; Peru-United States Leptospirosis Consortium. Leptospirosis: a zoonotic disease of global importance. *Lancet Infect Dis*. 2003;3(12):757–771.
8. Corwin A, Ryan A, Bloys W, et al. A waterborne outbreak of leptospirosis among United States military personnel in Okinawa, Japan. *Int J Epidemiol*. 1990;19(3):743–748.
9. Faine S, Adher B, Bloin C, et al, eds. *Leptospira and Leptospirosis*. 2nd ed. Melbourne, Australia: MedSci; 1994:199–205.
10. Kessler RC, Petukhova M, Sampson NA, et al. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res*. 2012;21(3):169–184.
11. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
12. Canli T. Reconceptualizing major depressive disorder as an infectious disease. *Biol Mood Anxiety Disord*. 2014;4:10.
13. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446–457.
14. Liu Y, Ho RC, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. *J Affect Disord*. 2012;139(3):230–239.
15. Dean B, Tawadros N, Scarr E, et al. Regionally-specific changes in levels of tumour necrosis factor in the dorsolateral prefrontal cortex obtained postmortem from subjects with major depressive disorder. *J Affect Disord*. 2010;120(1–3):245–248.
16. Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, et al. Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. *Mol Psychiatry*. 2011;16(7):751–762.
17. Chiu CH, Lin CL, Lee FY, et al. Leptospirosis and peripheral artery occlusive disease: a nationwide cohort analysis. *Medicine (Baltimore)*. 2016;95(11):e3127.
18. Chung WS, Chu YH, Lin CL, et al. Increased risk of acute coronary syndrome among leptospirosis patients: A nationwide cohort

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2017 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

analysis. *Int J Cardiol*. 2015;184:576–580.
19. Database NHIR. National Health Insurance Research Database Web site. http://nhird.nhri.org.tw/en/index.html. 2015.
20. Chen YG, Lin CL, Dai MS, et al. Risk of acute kidney injury and long-term outcome in patients with acetaminophen intoxication: a nationwide population-based retrospective cohort study. *Medicine (Baltimore)*. 2015;94(46):e2040.
21. Chung WS, Lin CL. Comorbid risks of deep vein thrombosis and pulmonary thromboembolism in patients with chronic pancreatitis: a nationwide cohort study. *J Thromb Haemost*. 2016;14(1):98–104.
22. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med*. 2008;358(1):55–68.
23. Alexopoulos GS, Meyers BS, Young RC, et al. 'Vascular depression' hypothesis. *Arch Gen Psychiatry*. 1997;54(10):915–922.
24. Newman SC. The prevalence of depression in Alzheimer's disease and vascular dementia in a population sample. *J Affect Disord*. 1999;52(1–3):169–176.
25. House A, Dennis M, Mogridge L, et al. Mood disorders in the year after first stroke. *Br J Psychiatry*. 1991;158:83–92.
26. Fujikawa T, Yanai I, Yamawaki S. Psychosocial stressors in patients with major depression and silent cerebral infarction. *Stroke*. 1997;28(6):1123–1125.
27. Coffey CE, Figiel GS, Djang WT, et al. Leukoencephalopathy in elderly depressed patients referred for ECT. *Biol Psychiatry*. 1988;24(2):143–161.
28. Coffey CE, Figiel GS, Djang WT, et al. White matter hyperintensity on magnetic resonance imaging: clinical and neuroanatomic correlates in the depressed elderly. *J Neuropsychiatry Clin Neurosci*. 1989;1(2):135–144.
29. Dolan RJ, Poynton AM, Bridges PK, et al. Altered magnetic resonance white-matter T1 values in patients with affective disorder. *Br J Psychiatry*. 1990;157:107–110.
30. Jokinen H, Kalska H, Ylikoski R, et al; LADIS group. MRI-defined subcortical ischemic vascular disease: baseline clinical and neuropsychological findings, the LADIS Study. *Cerebrovasc Dis*. 2009;27(4):336–344.
31. Thomas AJ, Ferrier IN, Kalaria RN, et al. A neuropathological study of vascular factors in late-life depression. *J Neurol Neurosurg Psychiatry*. 2001;70(1):83–87.
32. Van der Kooy K, van Hout H, Marwijk H, et al. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*. 2007;22(7):613–626.
33. Rybakowski JK, Wykretowicz A, Heymann-Szlachcinska A, et al. Impairment of endothelial function in unipolar and bipolar depression. *Biol Psychiatry*. 2006;60(8):889–891.
34. Richards D. Prevalence and clinical course of depression: a review. *Clin Psychol Rev*. 2011;31(7):1117–1125.

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2017 Copyright Physicians Postgraduate Press, Inc.