University of Louisville Journal of Respiratory Infections

ORIGINAL RESEARCH

Depression is associated with decreased severity and lower mortality in non-elderly hospitalized adults with influenza in the United States

Timothy L. Wiemken[1,2], PhD MPH; Daniel F Hoft[2], MD PhD; Jeffrey F Scherrer[3], PhD*

[1]Center for Health Outcomes Research, Saint Louis University, Saint Louis, MO, USA; [2]Division of Infectious Diseases, Allergy, and Immunology, Department of Internal Medicine, Saint Louis University; Department of Molecular Microbiology & Immunology, Saint Louis University, Saint Louis, MO, USA; [3]Department of Family and Community Medicine, Saint Louis University, Saint Louis, MO, USA

*timothy.wiemken@health.slu.edu

Abstract

Background: Depression is associated with risk for chronic disease, though its relationship with infectious diseases is less understood. Depression may modify the clinical outcomes of patients with infectious diseases such as influenza via its association with inflammation. The objective of this study was to evaluate the relationships between depression and clinical outcomes in non-elderly adults with influenza infection.

Methods: This was a secondary analysis of the Nationwide Inpatient Sample database, years 2012-2016. Hospitalized adults aged 18-65 admitted during each influenza season were included. Depression status was documented via ICD-10 codes. The association between depression and clinical outcomes (e.g. disease severity, length of hospital stay, and inpatient all-cause mortality) were evaluated using multivariable regression modeling.

Results: A total of 44,292 patients were included, 12% with depression. After adjustment for confounding, non-elderly influenza patients with depression had a 3.8% decreased risk of a severe disease (95% CI: 1.9% - 5.7%; P<0.001), no difference in length of stay (Hazard Ratio: 0.99, 95% Confidence Interval 0.96 – 1.02), and lower all-cause in-hospital mortality versus those without depression (Odds Ratio=0.76; 95% CI 0.59 - 0.97; P=0.028).

Conclusions: This study suggests that in non-elderly hospitalized patients with influenza, depression is associated with a decreased severity of illness and acute mortality. Chronic inflammation in those with depression may enhance the ability of the immune response to limit influenza infection or reduce pathologic acute inflammation associated with influenza disease.

Recommended Citation:
Wiemken, Timothy L.; Hoft, Daniel F., Scherrer, Jeffrey F. (2020). "Depression is associated with decreased severity and lower mortality in non-elderly hospitalized adults with influenza in the United States," *The University of Louisville Journal of Respiratory Infections*: Vol. 4, Iss. 2, Article 1.

Received Date: March 8, 2020

Accepted Date: April 22, 2020

Published Date: May 1, 2020

Funding Source: The authors received no specific funding for this work.

Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

Introduction

Major depression is a well established risk factor for chronic disease and adverse outcomes in comorbid patients. [1] Among the most studied are the relationships between depression and increased risk for incident cardiovascular disease [1, 2] and type-2 diabetes [3, 4]. In comparison, the literature on depression and infectious diseases is less developed. Depression is associated with a significantly increased acquisition of the common cold [5], *Clostridium (Clostridioides) difficile* infection following total knee replacement surgery [6], bloodstream infection [7], enterovirus infection [8], and is associated with increased risk of infection following elective shoulder arthroplasty [9]. To date, there is limited evidence of the impact of depression on influenza illness and outcomes, though a review of the sparse literature concluded that there is an absence of evidence to support or refute a link between depression and risk for influenza acquisition. [10] There is strong support for an immunologic dysregulation in many patients with depression which could explain some of these increased risks. Depression-related immune dysregulation is also associated with a blunted response to vaccines as well as delayed immunity. [11, 12] Patients with depression have increased pro-inflammatory cytokines (e.g. Interleukin 6, Tumor Necrosis Factor alpha) [13, 14] resulting in release of acute phase proteins, chemokines, and adhesion molecules [15]; immune cell differentiation and recruitment; and a wide array of other impacts on the human body [16]. Given depression is associated with a dysregulated immune state, depressed patients may have

a differential disease severity or outcome after infection as well.

Understanding the relationships between depression and influenza is critical. Nearly 21% of adults in the United States will experience a major depressive episode in their lifetime [17] and depression is now the leading cause of disability worldwide [18]. Further, influenza results in substantial morbidity and mortality globally each year and influenza research is often limited to only the elderly population, leaving a dearth of evidence in non-elderly populations. [19] Further research is warranted to determine if this common mental illness is associated with increased severity of, or poor outcomes in patients with influenza infection. The objective of this study was to evaluate the association between depression and influenza severity and clinical outcomes in non-elderly adult patients hospitalized with influenza in the United States.

Methods

Study Design
This was a secondary analysis of data from the National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality. This database contains is a 20% stratified sample of approximately 6-8 million hospital discharges per year. [20]

Subjects: Inclusion/Exclusion Criteria
Inpatient stays of individuals aged 18 – 64 with a discharge diagnosis code (ICD-9 or ICD-10) for influenza, from 2012 through 2016 were included in the analysis. Data were limited to months during the peak months of the typical influenza season in the United States (November through March). Patients without an all patient refined diagnosis related group (APR-DRG) severity or mortality risk subclass were excluded from analysis.

Human Subjects Protection – Because data are de-identified and publicly available this study is considered exempt from IRB approval.

Variable Definitions
Exposure:
- Depression – Patients were classified as having depression if they had an ICD-9/10 code for depression diagnoses on discharge (see the Supplementary Appendix for detailed codes).

Outcomes:
- Severity – Severity of illness was defined using the all patient refined diagnosis related group (APR-DRG) severity measure as documented in the NIS database. [21] This measure reflects the extent of a patient's physiologic decompensation or loss of organ system function and is calculated through passing diagnosis and procedure codes through a complex multiphase algorithm developed by 3M Health Information Systems. The APR-DRG severity was dichotomized into severe (Major or Extreme Loss of Function) versus non severe (Minor or Moderate Loss of Function).
- Length of Stay – Length of stay was defined as the number of days from admission to discharge or death.
- Mortality – Mortality was defined as all-cause inpatient mortality before discharge as documented in the NIS database.

Covariates
The following variables were selected for adjustment in regression modeling due to their potential confounding effects: Age (restricted cubic spline with 4 knots), gender, ICD-9/ICD-10 codes for diagnosis of pneumonia, nicotine dependence, anxiety disorder, and alcohol use disorder (see Appendix for detailed definitions), APR-DRG Severity (for mortality and length of stay models), APR-DRG mortality risk [21], quartile of median household income of patients zip code of residence, and 2017 AHRQ Elixhauser Weighted Comorbidity Index [22].

Statistical Analysis
Categorical variables were described with frequencies and percentages, while continuous variables were described with means and standard deviations or medians with interquartile ranges, as appropriate. Bivariable comparisons between depressed and non-depressed patients were made using Chi-squared or Fisher's Exact tests, while independent samples t-tests or Mann-Whitney U-tests were used to compare differences in continuous variables.

To define the adjusted impact of depression on disease severity, a multivariable Poisson regression model with a robust error estimator was used. [23] In this model, independent variables included: presence of pneumonia, a restricted cubic spline with 4 knots of the patient's age, nicotine dependence, anxiety disorder, gender, alcohol use disorder,

Table 1. Baseline characteristics of adult, non-elderly inpatients with influenza, November - March, 2012-2016 in the United States.

	Depressed n=4952	Non Depressed n=37588	P-value
Age, mean (SD)	50.72 (10.69)	47.41 (12.83)	<0.001
Female gender, n (%)	3286 (66.4)	20321 (54.1)	<0.001
Pneumonia, n (%)	1582 (31.9)	11818 (31.4)	0.481
Nicotine dependence, n (%)	2045 (41.3)	12090 (32.2)	<0.001
Alcohol use disorder, n (%)	253 (5.1)	1536 (4.1)	0.001
Anxiety, n (%)	2039 (41.2)	3500 (9.3)	<0.001
APRDRG Severity of Illness, n (%)			<0.001
Minor loss of function	446 (9.0)	4990 (13.3)	
Moderate loss of function	1756 (35.5)	14064 (37.4)	
Major loss of function	1917 (38.7)	12370 (32.9)	
Extreme loss of function	833 (16.8)	6164 (16.4)	
APRDRG Risk of Mortality, n (%)			<0.001
Minor likelihood of death	1940 (39.2)	16934 (45.1)	
Moderate likelihood of death	1260 (25.4)	8717 (23.2)	
Major likelihood of death	1233 (24.9)	7834 (20.8)	
Extreme likelihood of death	519 (10.5)	4103 (10.9)	
Median household income of residential zip code, n (%)			<0.001
1	1564 (32.1)	13104 (35.7)	
2	1286 (26.4)	9416 (25.6)	
3	1176 (24.2)	8069 (22.0)	
4	842 (17.3)	6166 (16.8)	
Weighted Elixhauser (AHRQ) Index, n (%)			<0.001
<0	2000 (40.4)	5764 (15.3)	
0	195 (3.9)	4205 (11.2)	
1-4	562 (11.3)	5713 (15.2)	
≥5	2195 (44.3)	21906 (58.3)	

• APRDRG: All Patient Refined Diagnosis Related Group

• AHRQ: Agency for Healthcare Research and Quality

APR-DRG risk of mortality, the quartile of median household income of the patients zip code of primary residence, and the weighted version of the grouped Elixhauser Comorbidity Index using the Agency for Healthcare Research and Quality (AHRQ) algorithm. [22] To assess the adjusted impact of depression on length of hospital stay and account for patients who died before discharge, competing risks regression was used. [24] All variables described above, as well as the severity of illness (APR-DRG Severity) were used for adjustment. To assess the impact of depression on in-hospital mortality, a multivariable logistic regression model was used. The same variables as documented for the length of stay model were included as covariates. Variance inflation factors, tolerance statistics, and correlation coefficients were used to evaluate the presence of multicollinearity before all regression modeling. R v3.6.1 (R Foundation for Statistical Computing, Vienna Austria) was used for all analyses.

Results

A total of 42,540 hospitalized adult, non-elderly patients with influenza were included in the analysis; 4,952 (12%) with a diagnosis code for depression and 37,588 (88%) without. Baseline socio-demographic and clinical features of patients stratified by the presence or absence of depression diagnosis can be seen in **Table 1**.

Several statistically significant differences in characteristics were identified between depressed and non-depressed hospitalized non-elderly adults with influenza. Depressed patients were slightly older (mean age 50.7 (SD ±10.7) years) compared to patients without depression (mean age 47.4 years (SD ±12.8, P<0.001). Patients with depression vs. those without were more likely to be female (66% vs 54%, P<0.001), have nicotine dependence (41% vs 32%, P<0.001), have alcohol use disorder (5% vs 4% (P=0.001), and an anxiety disorder (41% vs 9%, p<0.001). Depressed patients had a decreased unadjusted mortality versus non depressed patients (1.7% vs 2.7%, P<0.001).

As depicted in **Table 2**, non-elderly influenza patients with depression were found to have a 3.8% decreased adjusted risk of a major or severe loss of function versus those without depression (95% CI: 1.9% - 5.7%; P<0.001). **Table 3** re-

Table 2. Results of the multivariable regression model for severity of illness for adult, non-elderly inpatients with influenza, November - March, 2012-2016 in the United States.

Variable	Risk Ratio	Lower 95% CI	Upper 95% CI	P-value
Depression	0.96	0.943	0.981	<0.001
Female gender	1.00	0.991	1.016	0.63
Age, spline 1	1.00	0.994	1.001	0.107
Age, spline 2	1.00	0.992	1.007	0.926
Age, spline 3	0.99	0.946	1.044	0.802
Age, spline 4	1.07	0.914	1.245	0.412
Nicotine dependence	0.98	0.968	0.994	0.005
Anxiety	0.96	0.947	0.981	<0.001
Alcohol use disorder	1.00	0.972	1.023	0.82
Pneumonia	1.19	1.175	1.206	<0.001
APR-DRG Mortality Risk Minor	REFERENCE	-	-	-
APR-DRG Mortality Risk Moderate	4.51	4.303	4.726	<0.001
APR-DRG Mortality Risk Major	6.96	6.651	7.291	<0.001
APR-DRG Mortality Risk Extreme	6.24	5.939	6.552	<0.001
Median Household Income of Zip Code Quartile 1	REFERENCE	-	-	-
Median Household Income of Zip Code Quartile 2	1.00	0.987	1.020	0.704
Median Household Income of Zip Code Quartile 3	1.02	1.004	1.038	0.017
Median Household Income of Zip Code Quartile 4	1.02	0.997	1.035	0.104
Weighted Elixhauser (AHRQ) Index <0	REFERENCE	-	-	-
Weighted Elixhauser (AHRQ) Index 0	0.95	0.927	0.970	<0.001
Weighted Elixhauser (AHRQ) Index 1-4	0.91	0.873	0.954	<0.001
Weighted Elixhauser (AHRQ) Index ≥5	0.97	0.942	1.00	0.048

• APRDRG: All Patient Refined Diagnosis Related Group

• AHRQ: Agency for Healthcare Research and Quality

ports the results of competing risks regression for evaluation of adjusted associations between depression and length of hospital stay. Non-elderly influenza patients with depression had no change in length of stay (adjusted Hazard Ratio of discharge 0.99, 95% Confidence Interval 0.96 – 1.02). As depicted in **Table 4**, non-elderly influenza patients with depression had lower all-cause in-hospital mortality versus those without depression (adjusted Odds Ratio=0.76; 95% CI 0.59 - 0.97; P=0.028).

Discussion

In a large sample of non-elderly hospitalized patients with influenza infection, those with depression diagnoses had a decreased risk of more severe disease and a lower odds of inpatient mortality, but showed no difference in length of hospital stay. The relationship between depression and severity of disease was statistically significant, but the magnitude of the association was small and not likely to be clinically meaningful. This limited impact could be due to more severe illness in general regardless of depression status as indicated by the need for hospitalization. This magnitudue may be more pronounced in outpatient settings where severity of illness may have a wider distribution. It is also possible that by selecting a younger age cohort, we have selected for more severe hospitalized influenza cases.

While the lower risk of mortality in patients with depression is seemingly paradoxical and is in disagreement with one study in the Veterans Health Administration [25], the results may be consistent with the pathophysiology of influenza mortality. Depression is known to be associated with immune dysregulation, with many individuals suffering from this condition having increased baseline pro-inflammatory cytokines (e.g. Interleukin-6), and other inflammatory markers [13-15, 26]. Since death due to influenza is often associated with an overexuberant inflammatory response to infection rather than an overwhelming disseminated infection [27], patients with an already inflamed state may have negative regulatory networks activated which protect against excessive increases in inflammation. This negative feedback may prevent severe immunopathologic responses to influenza infection. [28] As an example, patients with lower respiratory tract infections such as pneumonia (a common complication of influenza infection) are at increased risk of myocardial infarction. [29] This is possibly due to the inflammatory response of the acute respiratory infection dislodging atherosclerotic plaques, resulting in infarction. If the inflammatory response post infection is not substantially different from

Table 3. Results of the multivariable competing risks regression model for length of hospital stay (time to discharge) of adult, non-elderly inpatients with influenza, November - March, 2012-2016 in the United States.

Variable	Hazard Ratio	Lower 95% CI	Upper 95% CI	P-value
Depression	0.99	0.961	1.019	0.470
Female gender	0.97	0.950	0.986	0.001
Age	0.996	0.995	0.996	<0.001
Nicotine dependence	0.75	0.639	0.870	<0.001
Anxiety	1.05	1.029	1.070	0.000
Alcohol use disorder	0.87	0.849	0.897	<0.001
Pneumonia	0.91	0.896	0.932	<0.001
APR-DRG Severity of Illness, Minor	REFERENCE	-	-	-
APR-DRG Severity of Illness, Moderate	0.81	0.782	0.832	<0.001
APR-DRG Severity of Illness, Major	0.56	0.535	0.579	<0.001
APR-DRG Severity of Illness, Extreme	0.27	0.259	0.289	<0.001
APR-DRG Mortality Risk Minor	REFERENCE	-	-	-
APR-DRG Mortality Risk Moderate	0.91	0.882	0.934	<0.001
APR-DRG Mortality Risk Major	0.84	0.807	0.867	<0.001
APR-DRG Mortality Risk Extreme	0.46	0.434	0.483	<0.001
Median Household Income of Zip Code Quartile 1	REFERENCE	-	-	-
Median Household Income of Zip Code Quartile 2	1.05	1.023	1.072	<0.001
Median Household Income of Zip Code Quartile 3	1.04	1.011	1.062	0.004
Median Household Income of Zip Code Quartile 4	1.03	1.003	1.059	0.031
Weighted Elixhauser (AHRQ) Index <0	REFERENCE	-	-	-
Weighted Elixhauser (AHRQ) Index 0	1.01	0.980	1.036	0.590
Weighted Elixhauser (AHRQ) Index 1-4	1.18	1.137	1.229	<0.001
Weighted Elixhauser (AHRQ) Index ≥5	1.10	1.067	1.138	<0.001

• APRDRG: All Patient Refined Diagnosis Related Group

• AHRQ: Agency for Healthcare Research and Quality

a baseline rate of inflammation, or this cascade is otherwise influenced by the baseline inflammation of a patient with depression, this event may not occur, and in-hospital death rates might be reduced.

Another rationale for our results includes the fact that depression in the NIS database is administratively coded for reimbursement on discharge. This means that the disease was significant for care during hospitalization, or was otherwise coded for a complex case. This may increase the likelihood of therapy for depression with various other medications, some of which could be anti-inflammatory. [30-34] Anti-inflammatory medications may improve the clinical outcomes of these patients similar to the impact of glucocorticoids, macrolide antibiotics, or other anti-inflammatory medications in patients with severe respiratory infection. [30-33] If depressed patients receive more anti-inflammatory medications than non-depressed patients, inpatient mortality could appear lower. This issue could also inject various confounding biases that were uncontrolled. It is also possible that there is a differential threshold for admitting a patient with depression and our results could be due to unadjusted artifacts of this issue, also similarly described in patients with obesity. [35]

One aspect not evaluated in this study includes the actual risk of influenza acquisition in the presence or absence of depression. The literature on this topic remains inconsistent and is dominated by small samples, with a systematic review concluding the quality of evidence does not support concluding there is an increased risk. [10] However, Segerstrom and colleagues revealed evidence that elderly patients with depression had reduced antibody response to multiple influenza strains compared to those without depression, suggesting a possible increase in risk of influenza acquisition. [12] In a separate study in 70 elderly participants, depression was associated with having significantly more influenza like symptoms, though this was no longer significant in multivariable analysis. [36] Without large prospective studies, this is likely to remain an unknown.

This study has several limitations. First, we did not have information on influenza vaccine history. Receipt of the influ-

Table 4. Results of the multivariable regression model for all-cause inpatient mortality of adult, non-elderly inpatients with influenza, November - March, 2012-2016 in the United States.

Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
Depression	0.76	0.594	0.971	0.028
Female gender	1.02	0.892	1.169	0.762
Age, spline 1	1.03	0.993	1.065	0.12
Age, spline 2	0.99	0.910	1.074	0.789
Age, spline 3	1.06	0.618	1.816	0.835
Age, spline 4	0.77	0.146	4.048	0.756
Nicotine dependence	0.75	0.639	0.870	<0.001
Anxiety	0.66	0.525	0.828	<0.001
Alcohol use disorder	1.17	0.900	1.512	0.246
Pneumonia	1.19	1.036	1.368	0.014
APR-DRG Severity of Illness, Minor	REFERENCE	-	-	-
APR-DRG Severity of Illness, Moderate	2.08	1.061	4.072	0.033
APR-DRG Severity of Illness, Major	3.93	1.930	8.021	<0.001
APR-DRG Severity of Illness, Extreme	22.2	10.805	45.627	<0.001
APR-DRG Mortality Risk Minor	REFERENCE	-	-	-
APR-DRG Mortality Risk Moderate	4.85	0.643	36.640	0.126
APR-DRG Mortality Risk Major	7.99	1.021	62.542	0.048
APR-DRG Mortality Risk Extreme	38.7	4.890	306.602	0.001
Median Household Income of Zip Code Quartile 1	REFERENCE	-	-	-
Median Household Income of Zip Code Quartile 2	0.91	0.768	1.087	0.308
Median Household Income of Zip Code Quartile 3	0.91	0.761	1.090	0.308
Median Household Income of Zip Code Quartile 4	0.91	0.746	1.108	0.347
Weighted Elixhauser (AHRQ) Index <0	REFERENCE	-	-	-
Weighted Elixhauser (AHRQ) Index 0	2.02	1.407	2.901	<0.001
Weighted Elixhauser (AHRQ) Index 1-4	1.33	0.737	2.394	0.345
Weighted Elixhauser (AHRQ) Index ≥5	0.99	0.609	1.625	0.983

• APRDRG: All Patient Refined Diagnosis Related Group

• AHRQ: Agency for Healthcare Research and Quality

enza vaccine is thought to, at minimum, a decreased severity of disease even when infected with influenza. [37] Mental illness has also been associated with failure to obtain vaccines, as well as decrease the immune response to some vaccines. [11, 12] Second, we were not able to include information on laboratory values which may be significant in the identification of subgroups affected differently by depressive state (e.g. cytokines and acute phase proteins). We also did not have information on the cause of death for these individuals. Although often difficult to ascertain, this information may assist in identifying subgroups affected differently by depression. Information on the number of days with respiratory symptoms before admission was not available in the NIS database. A delay in hospitalization for or with influenza will delay treatment. Since therapy with oseltamivir is only effective in the initial days of infection, a delay in seeking treatment will result in decreased therapeutic effectiveness resulting in potentially altered clinical outcomes. [38] Therefore, if depressed patients had a shorter duration of symptoms before hospitalization, they may be treated sooner resulting in improved clinical outcomes. Lack of information on anti-inflammatory medications (e.g. statins, steroids, etc) further limits the understanding of the relationship between depression and outcomes if depression is a result of hyperinflammation. Further, we did not have information on depression history and severity, and we lacked data on types of and compliance with treatment received including specific antidepressant medications, anti-psychotics and other psychotropics, some of which have recently been shown to alter feedback loops with depression (and likely inflammation). [39] Given the reliance on discharge ICD-9/10 codes, it is likely patients with depression or other covariates were misclassified. Our study focused on a younger age cohort, one typically not evaluated in studies of influenza and lower respiratory infection. Similar studies may have different results in elderly cohorts. However, defining depression in these older age groups could be challenging in the hospitalized patient. Finally, we did not have information on obesity status. Obesity is associated with nearly a two-fold increased risk for depression [40] and obesity is significantly more prevalent in those with depression [41]. This association could influence our results because

obesity is a known risk factor for severe influenza infection and increased mortality, since the 2009 H1N1 pandemic. [42, 43] Obesity may be an important effect modifier or have substantial interaction effects with depression due to the well-studied immune dysregulation in these patients. [28, 35]

There are many areas of research that are needed in the field of depression and influenza infection. Larger databases with more complete and precise covariates needed for adjustment (e.g. influenza vaccination history, other comorbid conditions, anti-inflammatory medications, obesity) will be necessary to more fully document these potential associations. Although secondary analytics will continue to uncover clues into the relationships between this debilitating disease with risk of and outcomes of infection, prospective studies are needed. For example, understanding the baseline inflammation of individuals prior to infection using novel causal machine learning models [44] may result in targeted approaches to influenza prevention and management. Associations between intestinal or respiratory microbiota, depression, and infection may also be warranted to define other novel areas for therapy. Recently, changes in the gut microbiota have been documented in patients with depression [45], though the directional impact is still unknown. Regardless, intestinal microbiota dysregulation increases systemic inflammation, and depression is preceded by systemic inflammation in some patients. [46-48] If gut microbiota induced systemic inflammation can trigger mood disorders, modulation of the gut microbiota may play a role in depression therapy and prevention of infection. [39]

In conclusion, this study suggests that in non-elderly hospitalized patients with influenza, depression is associated with a decreased severity of illness and acute mortality. Depression status may be an important marker of systemic inflammation critical to predicting clinical outcomes in these patients and should be evaluated more closely in more robust databases or prospective studies.

Acknowledgments

The authors would like to thank the following individuals for their expertise in NIS data and NIS administrative data management: Ms. Joanne Salas, Dr. Paula Buchanan, and Dr. Leslie Hinyard. We would also like to thank Dr. Leslie Hinyard for her editorial assistance.

Author Contributions

- Design of the protocol: TLW, JFS
- Statistical Analysis: TLW
- Primary Writing: TLW, DFH, JFS
- Critical Review: TLW, DFH, JFS

All authors have reviewed and approved the final version of the manuscript.

References

1. Thakore JH, editor. Physical consequences of depression. Routledge; 2001.
2. Elderon L, Whooley MA. Depression and cardiovascular disease. Prog Cardiovasc Dis. 2013 May-Jun;55(6):511–23. https://doi.org/10.1016/j.pcad.2013.03.010 PMID:23621961
3. Semenkovich K, Brown ME, Svrakic DM, Lustman PJ. Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. Drugs. 2015 Apr;75(6):577–87. https://doi.org/10.1007/s40265-015-0347-4 PMID:25851098
4. Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type II diabetes. A prospective population-based study. Diabetes Care. 1996 Oct;19(10):1097–102. https://doi.org/10.2337/diacare.19.10.1097 PMID:8886555
5. Shinkawa M, Yanai M, Yamaya M, Matsui T, Sasaki H. Depressive state and common cold. Lancet. 2000 Sep;356(9233):942. https://doi.org/10.1016/S0140-6736(05)73925-8 PMID:11036920
6. Gwam CU, George NE, Etcheson JI, Tarazi JM, Han GR, Griffith KM, et al. Clostridium difficile infection in the USA: incidence and associated factors in revision total knee arthroplasty patients. Eur J Orthop Surg Traumatol. 2019 Apr;29(3):667–74. https://doi.org/10.1007/s00590-018-2319-3 PMID:30350019
7. Askim Å, Gustad LT, Paulsen J, Reitan SK, Mehl A, Mohus RM, et al. Anxiety and depression symptoms in a general population and future risk of bloodstream infection: the HUNT study. Psychosom Med. 2018 Sep;80(7):673–9. https://doi.org/10.1097/PSY.0000000000000619 PMID:29923889
8. Liao YT, Hsieh MH, Yang YH, Wang YC, Tsai CS, Chen VC, et al. Association between depression and enterovirus infection: A nationwide population-based cohort study. Medicine (Baltimore). 2017 Feb;96(5):e5983. https://doi.org/10.1097/MD.0000000000005983 PMID:28151890
9. Mollon B, Mahure SA, Ding DY, Zuckerman JD, Kwon YW. The influence of a history of clinical depression on peri-operative outcomes in elective total shoulder arthroplasty: a ten-year national analysis. Bone Joint J. 2016

Jun;98-B(6):818–24. https://doi.org/10.1302/0301-620X.98B6.37208 PMID:27235526
10. Gharbawy D, Tadrous M, Suda K. Does depression lead to influenza? - A systematic literature analysis. J Affect Disord. 2012 Apr;138(1-2):41–5. https://doi.org/10.1016/j.jad.2011.12.037 PMID:22335890
11. Irwin MR, Levin MJ, Laudenslager ML, Olmstead R, Lucko A, Lang N, et al. Varicella zoster virus-specific immune responses to a herpes zoster vaccine in elderly recipients with major depression and the impact of antidepressant medications. Clin Infect Dis. 2013 Apr;56(8):1085–93. https://doi.org/10.1093/cid/cis1208 PMID:23413415
12. Segerstrom SC, Hardy JK, Evans DR, Greenberg RN. Vulnerability, distress, and immune response to vaccination in older adults. Brain Behav Immun. 2012 Jul;26(5):747–53. https://doi.org/10.1016/j.bbi.2011.10.009 PMID:22062498
13. Anisman H, Ravindran AV, Griffiths J, Merali Z. Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. Mol Psychiatry. 1999 Mar;4(2):182–8. https://doi.org/10.1038/sj.mp.4000436 PMID:10208451
14. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, et al. The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun. 2001 Sep;15(3):199–226. https://doi.org/10.1006/brbi.2000.0597 PMID:11566046
15. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. Brain Behav Immun. 2007 May;21(4):374–83. https://doi.org/10.1016/j.bbi.2007.01.010 PMID:17360153
16. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014 Sep;6(10):a016295. https://doi.org/10.1101/cshperspect.a016295 PMID:25190079
17. Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry. 2018 Apr;75(4):336–46. https://doi.org/10.1001/jamapsychiatry.2017.4602 PMID:29450462
18. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al.; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov;392(10159):1789–858. https://doi.org/10.1016/S0140-6736(18)32279-7 PMID:30496104
19. World Health Organization, World Health Organization. The top 10 causes of death. 2014. Fact sheet. 2018 May(310).
20. Rockville M. HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2012.
21. Averill RF, Goldfield N, Hughes JS, Bonazelli J, McCullough EC, Steinbeck BA, et al. All Patient Refined Diagnosis Related Groups (APR- DRGs). Version 20.0 Methodology Overview. Wallingford, CT: 3M Health Information Systems. 2003.
22. Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: the AHRQ Elixhauser comorbidity index. Med Care. 2017 Jul;55(7):698–705. https://doi.org/10.1097/MLR.0000000000000735 PMID:28498196
23. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004 Apr;159(7):702–6. https://doi.org/10.1093/aje/kwh090 PMID:15033648
24. Brock GN, Barnes C, Ramirez JA, Myers J. How to handle mortality when investigating length of hospital stay and time to clinical stability. BMC Med Res Methodol. 2011 Oct;11(1):144. https://doi.org/10.1186/1471-2288-11-144 PMID:22029846
25. Zivin K, Yosef M, Miller EM, Valenstein M, Duffy S, Kales HC, et al. Associations between depression and all-cause and cause-specific risk of death: a retrospective cohort study in the Veterans Health Administration. J Psychosom Res. 2015 Apr;78(4):324–31. https://doi.org/10.1016/j.jpsychores.2015.01.014 PMID:25697585
26. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol. 2011 Aug;11(9):625–32. https://doi.org/10.1038/nri3042 PMID:21818124
27. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012 Mar;76(1):16–32. https://doi.org/10.1128/MMBR.05015-11 PMID:22390970
28. Kahlon S, Eurich DT, Padwal RS, Malhotra A, Minhas-Sandhu JK, Marrie TJ, et al. Obesity and outcomes in patients hospitalized with pneumonia. Clin Microbiol Infect. 2013 Aug;19(8):709–16. https://doi.org/10.1111/j.1469-0691.2012.04003.x PMID:22963453
29. Ramirez J, Aliberti S, Mirsaeidi M, Peyrani P, Filardo G, Amir A, et al. Acute myocardial infarction in hospitalized patients with community-acquired pneumonia. Clin Infect Dis. 2008 Jul;47(2):182–7. https://doi.org/10.1086/589246 PMID:18533841
30. Horita N, Otsuka T, Haranaga S, Namkoong H, Miki M, Miyashita N, et al. Adjunctive systemic corticosteroids for hospitalized community-acquired pneumonia: systematic review and meta-analysis 2015 update. Sci Rep. 2015 Sep;5(1):14061. https://doi.org/10.1038/srep14061 PMID:26374694
31. Tagami T, Matsui H, Horiguchi H, Fushimi K, Yasunaga H. Antithrombin and mortality in severe pneumonia patients with sepsis-associated disseminated intravascular coagulation: an observational nationwide study. J Thromb Haemost. 2014 Sep;12(9):1470–9. https://doi.org/10.1111/jth.12643 PMID:24943516

32. Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. Jama. 2015 Feb 17;313(7):677-86.
33. Wunderink RG. Corticosteroids for severe community-acquired pneumonia: not for everyone. JAMA. 2015 Feb;313(7):673–4. https://doi.org/10.1001/jama.2015.115 PMID:25688777
34. Peyrani P, Wiemken TL, Metersky ML, Arnold FW, Mattingly WA, Feldman C, et al. The order of administration of macrolides and beta-lactams may impact the outcomes of hospitalized patients with community-acquired pneumonia: results from the community-acquired pneumonia organization. Infectious Diseases. 2018 Jan 2;50(1):13-20.
35. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. American heart journal. 2008 Jul 1;156(1):13-22. https://doi.org/10.1016/j.ahj.2008.02.014 PMID:18585492
36. Gidron Y, Hassid A, Yisrael H, Biderman A. Do psychological factors predict occurrence of influenza-like symptoms in vaccinated elderly residents of a sheltered home? Br J Health Psychol. 2005 Sep;10(Pt 3):411–20. https://doi.org/10.1348/135910704X20026 PMID:16238856
37. Godoy P, Romero A, Soldevila N, Torner N, Jané M, Martínez A, et al.; The Working Group On Surveillance Of Severe Influenza Hospitalized Cases In Catalonia. Influenza vaccine effectiveness in reducing severe outcomes over six influenza seasons, a case-case analysis, Spain, 2010/11 to 2015/16. Euro Surveill. 2018 Oct;23(43). https://doi.org/10.2807/1560-7917.ES.2018.23.43.1700732 PMID:30376915
38. Ramirez J, Peyrani P, Wiemken T, Chaves SS, Fry AM. A randomized study evaluating the effectiveness of oseltamivir initiated at the time of hospital admission in adults hospitalized with influenza-associated lower respiratory tract infections. Clin Infect Dis. 2018 Aug;67(5):736–42. https://doi.org/10.1093/cid/ciy163 PMID:29659754
39. McVey Neufeld KA, Bienenstock J, Bharwani A, Champagne-Jorgensen K, Mao Y, West C, et al. Oral selective serotonin reuptake inhibitors activate vagus nerve dependent gut-brain signalling. Sci Rep. 2019 Oct;9(1):14290. https://doi.org/10.1038/s41598-019-50807-8 PMID:31582799
40. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. Int J Obes Relat Metab Disord. 2003 Apr;27(4):514–21. https://doi.org/10.1038/sj.ijo.0802204 PMID:12664085
41. Pratt L, Brody D. Depression and obesity in the US adult household population, 2005-2010. NCHS Case brief, 167. Hyattsville (MD): National Center for Health Statistics; 2014.
42. Centers for Disease Control and Prevention (CDC). Hospitalized patients with novel influenza A (H1N1) virus infection - California, April-May, 2009. MMWR Morb Mortal Wkly Rep. 2009 May;58(19):536–41. PMID:19478723
43. Centers for Disease Control and Prevention (CDC). Intensive-care patients with severe novel influenza A (H1N1) virus infection - Michigan, June 2009. MMWR Morb Mortal Wkly Rep. 2009 Jul;58(27):749–52. PMID:19609249
44. Athey S, Tibshirani J, Wager S. Generalized random forests. Ann Stat. 2019;47(2):1148–78. https://doi.org/10.1214/18-AOS1709.
45. Cheung S, Goldenthal AR, Uhlemann AC, Mann JJ, Miller JM, Sublette ME. Systematic review of gut microbiota and major depression. Front Psychiatry. 2019 Feb;10:34. https://doi.org/10.3389/fpsyt.2019.00034 PMID:30804820
46. Brenchley JM, Douek DC. Microbial translocation across the GI tract. Annu Rev Immunol. 2012;30(1):149–73. https://doi.org/10.1146/annurev-immunol-020711-075001 PMID:22224779
47. Dinh DM, Volpe GE, Duffalo C, Bhalchandra S, Tai AK, Kane AV, et al. Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection. J Infect Dis. 2015 Jan;211(1):19–27. https://doi.org/10.1093/infdis/jiu409 PMID:25057045
48. Jørgensen SF, Trøseid M, Kummen M, Anmarkrud JA, Michelsen AE, Osnes LT, et al. Altered gut microbiota profile in common variable immunodeficiency associates with levels of lipopolysaccharide and markers of systemic immune activation. Mucosal Immunol. 2016 Nov;9(6):1455–65. https://doi.org/10.1038/mi.2016.18 PMID:26982597