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The association of unipolar depression with thirty-day mortality after hospitalization for infection: A population-based cohort study in Denmark

Dimitry S. Davydow MD, MPH [a,*], Anette Riisgaard Ribe MD PhD [b], Henrik Søndergaard Pedersen MSc [b], Mogens Vestergaard MD, PhD [b], Morten Fenger-Grøn MSc [b]

[a] Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA
[b] Research Unit for General Practice, Department of Public Health, Aarhus University, Aarhus, Denmark

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ABSTRACT

Objective: While depression is associated with higher risk of death due to chronic medical conditions, it is unknown if depression increases mortality following serious infections. We sought to determine if pre-existing unipolar depression is associated with increased mortality within 30 days after hospitalization for a serious infection.
Methods: We conducted a population-based cohort study of all adults hospitalized for an infection in Denmark between 2005 and 2013. Pre-existing unipolar depression was ascertained via psychiatrist diagnoses or at least two antidepressant prescription redemptions within a six month period. Our primary outcome was all-cause mortality within 30 days after infection-related hospitalization. We also studied death due to infection within 30 days after admission.
Results: We identified 589,688 individuals who had a total of 703,158 hospitalizations for infections. After adjusting for demographics, infectious diagnosis and time since infection, socioeconomic factors and comorbidities, pre-existing unipolar depression was associated with slightly increased risk of all-cause mortality within 30 days after infection-related hospitalization (Mortality Rate Ratio [MRR]: 1.07, 95% Confidence Interval [95% CI]: 1.05, 1.09). The association was strongest among persons who initiated antidepressant treatment within one year before the infection (MRR: 1.30, 95% CI: 1.25, 1.35). Pre-existing unipolar depression was associated with increased risk of death due to sepsis (MRR: 1.30, 95% CI: 1.17, 1.44), pneumonia (MRR: 1.23, 95% CI: 1.16, 1.29) and urinary tract infection (MRR: 1.25, 95% CI: 1.08, 1.44) after adjusting for demographics, infectious diagnosis at admission and time since infection.
Conclusions: Pre-existing unipolar depression is associated with slightly increased mortality following hospitalization for an infection.

1. Introduction

Depression is a highly prevalent psychiatric disorder throughout the world [1]. It is a leading cause of years lived with disability [1], and individuals with depression suffer more chronic medical disease-related sequelae than those without depression [2]. Notably, a recent meta-analysis identified that having a diagnosis of depression is associated with a 71% greater risk for premature all-cause mortality [3]. Importantly, a nationwide cohort study from Denmark identified that unipolar depression is associated with a decreased life expectancy of 14 years in men and 10 years in women [4]. While this study found that depression was strongly associated with increased risk for death due to suicide and accidents [4], the absolute number of deaths attributable to depression was highest for medical diseases [4].

Yet, while depression is known to be associated with increased risk for mortality in patients with chronic diseases such as diabetes and coronary artery disease [5–7], it remains unclear whether death following acute medical illnesses may explain some of the association between depression and reduced life expectancy. Depression has been found to be associated with increased risk for hospitalization for serious infections [8], but it is unknown if pre-existing depression is a risk factor for death following serious infections. This possibility is important to consider since depression has been shown to be associated with increased levels of inflammatory cytokines [9], a contributing factor in the development of sepsis in the face of infection [10], from which nearly 1/3rd of patients do not survive [11]. Furthermore, a recent study identified that individuals with schizophrenia or bipolar disorder have higher mortality following hospitalization for an infection [12]. Since unipolar depression is more prevalent in the general population than

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Box 356560, 1959 NE Pacific St, Seattle, WA 98195, United States.
E-mail address: ddavydo1@uw.edu (D.S. Davydow).

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schizophrenia or bipolar disorder [13,14], and evidence-based depression treatments are being increasingly integrated into general practice settings world-wide [15,16], identifying depression as a potential risk factor for death following hospitalization for a serious infection could have important public health impact.

The present study utilizes data from a large population-based cohort of Danish adults to determine if pre-existing unipolar depression is associated with increased risk of mortality within 30 days after hospitalization for a serious infection. We hypothesized that pre-existing depression would be associated with a higher relative risk of death when compared to individuals without pre-existing depression.

2. Methods

2.1. Population

We conducted a population-based cohort investigation utilizing data from nationwide Danish registries. Our cohort included all living persons aged 15 years or older, residing in Denmark for at least 10 years (to ensure continuous information on depression), and hospitalized for an infection at least once between January 1, 2005 and December 1, 2013. We constructed our cohort using information from two registries: 1) the Danish Civil Registration System [17], which includes data on sex, birth date, vital status and immigration into or from Denmark since January 1, 1968, and 2) the Danish National Patient Register [18], which contains information on all medical hospitalizations since January 1, 1977 and outpatient visits since January 1, 1995. In the Danish Civil Registration System, Danish residents are each assigned a unique personal identification number which allows for linkage to person-level data [17].

We used the Danish National Patient Register to identify hospitalizations for infection (i.e., primary or secondary discharge diagnoses of infection) and categorized them according to the type of infection resulting in hospitalization (see Appendix 1).

The Danish Data Protection Agency and the Danish Health and Medicine Authority approved the study protocol. Requirement for informed consent was waived.

2.2. Primary independent variable

Our primary independent variable of interest was unipolar depression as determined by either psychiatric diagnosis or filling at least two antidepressant prescriptions within a six month time-frame. Unipolar depression diagnoses were obtained from the Danish Psychiatric Central Register (see Appendix 2) [19], which includes data on all psychiatric hospitalizations since January 1, 1969 and outpatient psychiatric visits since January 1, 1995 [19]. Importantly, before December 31, 1993, register-based diagnoses were based on the Danish version of the International Classification of Diseases, 8th Revision (ICD-8) [20]. From January 1, 1994 onward, the Danish version of the ICD-10 [21] was used. Prescription redemptions for antidepressant medications (i.e., selective serotonin re-uptake inhibitors (SSRIs), monoamine oxidase inhibitors, and other non-tricyclic (TCA) antidepressants, see Appendix 2) were identified using the Danish National Prescription Registry [22]. This registry includes information on all prescriptions dispensed at Danish pharmacies since 1995, including purchase date and classification of drugs according to the Anatomical Therapeutic Chemical Classification [23]. We excluded TCA prescriptions from our definition of depression due to their frequent use for insomnia and/or pain. Additionally, we excluded bupropion and trazodone prescriptions since neither were approved for depression treatment in Denmark during the study period.

Since depression can be an aspect of bipolar disorder and is a common comorbidity in schizophrenia [24,25], we excluded individuals with a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder. We used data from the Danish Psychiatric Central Register (see Appendix 3) [21] to identify persons with bipolar disorder, schizophrenia or schizoaffective disorder diagnoses, censoring them at the date of diagnosis.

2.3. Outcomes of interest

Our primary outcome of interest was all-cause mortality within 30 days after hospitalization for an infection occurring between 2005 and 2013, and was identified using the Danish Civil Registration System [17]. As a secondary outcome, we also examined death due to infection within 30 days after hospitalization using data from the Danish Register of Causes of Death [26]. Deaths due to infections were categorized in the same manner as hospitalizations for infections.

2.4. Socioeconomic factors, comorbid medical conditions, and substance abuse disorders

Data on civil status and education was obtained from Statistics Denmark (see Appendix 4) [27,28]. We categorized civil status as living with a partner (i.e., married, registered partnership or cohabitation) or living alone (i.e., living without a partner, including widows/widowers). We classified maximum educational attainment into three categories based on the United Nations Educational, Scientific and Cultural Organization's International Standard Classification of Education: low (<10 years), middle (10–15 years), and high (>15 years) [29].

We obtained data from the Danish National Patient Register on comorbid medical conditions based on the Charlson Comorbidity Index (CCI) [30] categories (see Appendix 5), with two exceptions. Data on diabetes diagnoses was obtained from the Danish National Diabetes Register between January 1, 1990 and December 31, 2013 (see Appendix 6) [31]. Chronic pulmonary disease was defined as either a diagnosis based on the CCI category obtained from the Danish National Patient Register or ≥ two prescriptions redeemed within a six month period for medications treating obstructive airway diseases (see Appendix 7) as obtained from the Danish National Prescription Registry.

Information on substance use (except tobacco use) disorders was obtained from the Danish Psychiatric Central Register or the Danish National Patient Register (see Appendix 8).

2.5. Statistical analysis

In our analyses, individuals hospitalized for an infection were censored on date of death, date of emigration, December 31, 2013, or 30 days after admission, whichever came first.

We compared persons with pre-existing unipolar depression to those without depression using log-linear Poisson regression models to estimate mortality rate ratios (MRRs) for all-cause mortality within 30 days after hospitalization for an infection. In these models, the logarithm of person-days was used as an offset variable. Hospitalizations were the unit of analysis in all models. Corresponding *P* values and 95% Confidence Intervals (95% CIs) were estimated using likelihood ratio tests. Adjustments for age were performed using categories spanning two years (e.g., 15, 17, …, maximum) and for calendar period as a binary category (i.e., 2005–2009 versus 2010–2013). In order to address missing data on education, we conducted multiple imputation using ten imputed data sets according to methods developed by Rubin [32].

To determine the risk of all-cause mortality within 30 days after hospitalization for an infection associated with pre-existing unipolar depression, we fitted three risk models, adjusting sequentially as follows: 1) demographics (i.e., age at infection, sex, and calendar period) as well as infection characteristics (i.e., infection type, days since infection, and the interaction of infection type and days since infection); 2) socioeconomic factors (i.e., education and civil status); and 3) comorbidities (comorbid medical conditions and substance use disorders each entered individually), our primary model.