**Depressive Symptoms and Short-term Outcomes after Medical Hospitalization**

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Department of Medicine

University of Alberta

## Abstract

This thesis consists of 2 closely linked projects that evaluate the importance of depressive symptoms (hereafter, for brevity, referred to as "depression") for short-term prognosis after general medical hospitalizations. **Project 1** systematically reviews the literature to examine whether depression identifies increased risk of short-term adverse events (such as the composite endpoint of death or readmission within 30-days) post-discharge. Using prior literature and potential confounders identified in Project 1, **Project 2** uses primary data collection to overcome limitations of previous studies and evaluates the prognostic utility and independent association between depression as defined by the PHQ-9 and the carefully adjusted risk of short-term adverse events post-discharge from general internal medicine (GIM) wards.

In **Project 1**, 18 papers were reviewed, including published and unpublished data retrieved for up to 3397 patients with 30-day follow-up. It was determined that depression affected one-third of patients hospitalized for an acute medical reason (median 32%) and predicted both higher rates of readmission (20% vs. 14%, RR 1.73, 95%CI 1.16-2.58, n=2433) and mortality (3% vs. 2%, RR 2.13, 95%CI 1.31-3.44, n=3397) within 30-days post-discharge, with similar results observed at 90-days; that relatively few valid studies have examined short-term outcomes, and that most prior studies are limited to disease-specific patient populations (vs. unselected general medical cohorts) and lack repeated depression measures post-discharge. In **Project 2**, it was found that depression was common (26% of inpatients), largely unrecognized, often persisted for months post-discharge, and independently predicted an adjusted 2-fold increased risk of short-term death or readmission post-discharge over and above the best available risk-

prediction tools. The findings from my thesis support the concept that clinicians should systematically screen patients for depression before discharge using validated tools and highlights two future directions for research: (1) designing post-discharge interventions that target depressed patients and (2) determining if treating depression reduces rates of short-term death or readmission in these patients.

**Preface**

The systematic review and meta-analysis in Chapter 2 has been submitted for publication as Pederson JL, Warkentin LM, Majumdar SR, McAlister FA. Depressive symptoms are associated with higher rates of readmission or mortality in adults discharge after a medical hospitalization: A systematic review and meta-analysis. SRM, FAM, and myself were responsible for the design and conduct of the study, the analysis and interpretation of the data, and the drafting of the manuscript. LMW and myself were responsible for data acquisition. SRM and FAM were responsible for study supervision.

The PROACTIVE research project, for which Chapter 3 of this thesis is part, was approved by the Health Research Ethics Board at the University of Alberta (project ID Pro00036880). All participants provided written informed consent. Chapter 3 has been submitted for publication as Pederson JL, Majumdar SR, Forhan M, Johnson JA, McAlister FA, for the PROACTIVE Investigators. Depression is associated with poorer short-term outcomes after discharge from medical wards: A multi-site prospective cohort study. SRM, FAM, and myself were responsible for the design and conduct of the study. Myself and the PROACTIVE Investigators were responsible for data acquisition. I was responsible for data analysis, with assistance from SRM and FAM. JLP and FAM were responsible for the writing of the manuscript and critical revisions were made by all authors. FAM and SRM were responsible for study supervision and funding was provided by FAM, SRM, and JAJ.

To my peers and the young women who inspire me,

Erin and Kaley Pederson

Dani Wiebe, Bethany Lyons, and Whitney Haynes

**Acknowledgements**

I would like to thank my supervisors, Finlay McAlister and Sumit Majumdar, for their guidance on research 'from the ground-up' –from the development of baseline questionnaires to final revisions before publication, the many hours spent in between, and advice on best approach for each phase. Also, thank you for providing jokes, as needed.

In addition, I would like to thank my committee member, Mary Forhan, for her support, our study coordinator, Miriam Fradette, for supervision on study operationalization and data acquisition, statisticians, Jeff Bakal and Erik Youngson, for data and analytic support, Dale Storie, MLS, for his assistance during literature searches for the systematic review, Jeff Johnson for external support within the PROACTIVE sphere as well as Lindsey Warkentin for peer mentorship within the graduate program.

I would like to acknowledge several primary study authors (Drs. Nancy Frasure-Smith, Andriana I. Papaioannou, and Pere Almagro, and Mr. Philip G. Jones) for their retrieval and contribution of unpublished data for Project 1 and Dr. James Hanley for his assistance in data recovery methods.

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# Chapter 1 Introduction

## *i. Short-term readmissions are a major driver of healthcare expense*

Short-term readmissions or early deaths after hospital discharge are common, costly, and of increasing national priority. Between 10% to 40% of patients are readmitted within 30-days after being discharged from hospital.[1–3] This accounts for at least 11% of total hospitalization costs in Canada.[4] In the U.S., unplanned short-term readmissions were estimated to cost $17 billion in 2004 –approximately 17% of all hospital payments received from Medicare.[4] Renewed efforts that result in even small reductions in readmissions may improve quality of care and substantially reduce costs.[5]

General Internal Medical (GIM) patients account for approximately 65% of all 30-day readmissions.[4] Overall, 13% of medical patients bounce-back within 30-days, that is 1.6 times the Canadian average (9%) and over 2 times the rates of surgical (7%), obstetric (7%), and paediatric (2%) patients.[4] Moreover, subsequent readmissions in medical patients were found to require 42% ($3,117 on average) more expensive inpatient care than the initial hospitalizations while non-medical readmissions were far less expensive.[4] Thus, it is especially important to understand patterns of utilization and early adverse events in medical patients.

## *ii. Factors that may influence patient readmission*

Readmissions are complex and multi-factorial. Studies of readmissions generally focus on potential causes at the level of the patient (e.g. age, sex, income, clinical condition, comorbidity), hospital (e.g. patterns of length of stay, size), and/or community (e.g. availability of post-acute care, neighbourhood income).[4,6] All-cause readmissions are a

common measure of evaluation and are considered planned or unplanned. Planned readmissions reflect a continuity of clinical care[7] while unplanned readmissions result from relapse of diseases or other acute events or circumstances that require hospital (re)admission.[2,8] Most (at least 83% [9]) all-cause readmissions to medical wards are unplanned while the top 3 most responsible admitting diagnoses in both Canada and the US are exacerbations of heart failure or COPD and acute episodes of pneumonia.[1,4,8]

Further, some unplanned readmissions may be potentially preventable, though estimates vary from 9% to 59%, depending on the study.[3,4,10,11] In a systematic review of determinants of preventable readmission, the predominant indicator was general ill health (as reported by the Charlson Comorbidity Index or Elixhauser Index scales, worsening of index condition, poor self-rated health, or other).[6] The authors note that while patient level factors dominated most research, many of these patient characteristics are immutable and usually not under the control of providers or their hospitals.[6] There is a need to better understand the role of avoidability in readmissions and an urgent need to identify factors that may be targeted or modified in interventions intended to reduce early deaths and readmissions.[3,6,11]

### *iii. Factors that may influence interventions*

Indeed, many interventions have been tested to reduce readmission or mortality shortly after hospital discharge but the results have been mixed. Interventions have included pre-discharge patient education and discharge planning, enhanced post-discharge follow-up, or transitional patient centred and same-provider continuity.[4,12] Many of these tested interventions have had little-to-no effect on patient outcomes.[12–14]

Risk stratification may increase the effectiveness of post-discharge interventions by targeting those at highest risk of adverse events,[15] but currently available risk prediction rules are less than perfect. Most risk factors included in these models reflect older age and comorbidities ("frailty") and prior healthcare utilization and are usually derived by using administrative claims data rather than clinical information.[16] Thus, it is important to determine the "value-added" of introducing clinical information into these risk prediction models and to identify novel and potentially modifiable risk factors that are not (yet) routinely captured.[8,16]

### *iv. Depression may be a potentially modifiable novel risk-factor for short-term outcomes*

Depression is common in adults with chronic disease and associated with poor prognosis.[17,18] About 30-40% of hospitalized adults report "depression," depending on how depression is defined.[19,20] This rate of depression is 2-3 times higher than the rate of 5-13% that is observed in primary care settings.[21] Symptoms of depression may range from minor depression (sub-threshold episodic depression) to dysthymia (mild persistent symptoms) or to major depressive disorders (MDD).[22] The various levels of depression have been directly and in "dose-dependent" fashion been associated with disease progression in heart failure and post-myocardial infarction, disability, foreshortened life expectancy and other adverse events.[23–27]

Moreover, depression is often poorly detected and under-treated in hospital despite the availability of many different evidence-based pharmacologic and non-pharmacologic treatments.[28–30] A review of 37 studies that examined detection of depression found low rates of clinical recognition by non-psychiatrists in every clinical setting examined.[31] For example, acute

care physicians had a 67-91% probability of missing cases of symptomatic depression in hospital (9-33% sensitivityand 82-92% specificity).[31]

Further to this, depression may be an under-recognized risk factor for short-term death or readmission post-discharge, and few readmission risk prediction models have examined depression as a potential predictor. Indeed, of 26 models to predict risk of hospital readmission,[16] only 5 specified a history of depression (based on chart review or claims data),[32–36] and none incorporated current symptoms of depression.

### *v. Objectives*

We examined whether current depression is an under-recognized prognostic factor for short-term (30- and 90-day) all-cause readmission or mortality after medical hospitalization. **Project 1** systematically reviewed all of the available published evidence on the associations between depression and short-term risk of death or readmissions post-discharge as well as guiding our study design and analysis so as to overcome limitations of previous studies. **Project 2** built upon this work and used prospective data collection in hospitalized medical patients to evaluate the independent prognostic value of depression with respect to post-discharge adverse events as well as defining the prevalence (in-hospital) and persistence (post-hospital) of symptomatic depression in a high-risk group of patients.

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# Chapter 2 Depressive symptoms are associated with higher rates of readmission or mortality in adults discharged after a medical hospitalization: A systematic review and meta-analysis[1]

[1] *A version of this chapter has been submitted for publication.*

**ABSTRACT**

**Objective** To systematically evaluate whether depression is a prognostic factor for 30-day readmission or mortality in medical patients discharged from hospital.

**Design** Systematic review and meta-analysis of studies appraised using the Newcastle-Ottawa Scale and analyzed using random-effects models.

**Data Sources** CINAHL, MEDLINE, EMBASE, PsychINFO, and PUBMED were searched through January 2015.

**Eligibility Criteria for Selecting Studies** We identified any study that used diagnostic interviews or validated scales to detect depression before the time of discharge and compared post-discharge outcomes between patients with versus without depression. Included articles were only those peer-reviewed longitudinal with at least 30-day follow-up for readmission or mortality in patients discharged from medical wards after treatment for non-psychiatric admission. Two authors abstracted data on study characteristic and risk estimates. Unpublished data was sought from all primary study authors.

**Results** The initial search yielded 4066 papers; 133 underwent full review. We identified 18 longitudinal studies; 14 were meta-analyzable. One-third of 6104 patients discharged from acute care medical wards were depressed (median 32%, interquartile range 27% to 40%). Overall, 395 of 2433 (16.2%) patients were readmitted and 69 of 3397 (2.0%) patients died within 30-days. Compared to those without depression, medical patients discharged with depression were more

likely to be readmitted (20.4% vs. 13.7%, RR 1.73, 95%CI 1.16-2.58) or die (2.8% vs.1.5%, RR 2.13, 95%CI 1.31-3.44) within 30-days. Results were similar at 90-days: 39.8% vs. 31.0% readmitted (RR 1.68, 95%CI 1.13-2.50, n=1543 patients) and 7.7% vs. 4.1% died (RR 2.01, 95%CI 1.47-2.76, n=784 patients).

**Conclusions** Depression is common among hospitalized medical patients and can be used to identify individuals at increased risk of short-term all-cause readmission or early death after discharge.

## INTRODUCTION

Between 10% to 40% of patients are readmitted after being discharged from hospital[1–3] and as many as another 25% return to the Emergency Department within 30-days.[4,5] This creates substantial burden on the health care system.[2,6,7] Various interventions have been tried to improve the quality of discharge transitions and reduce readmission rates, but results thus far have been inconsistent and generally disappointing.[8–10] Targeted delivery of interventions to those at highest risk might improve the effectiveness of these efforts and reduce costs. However, current readmission risk assessment models are only moderately predictive, suggesting the presence of unrecognized risk factors.[11,12]

Active depression might represent a potentially modifiable independent predictor of adverse short-term hospital outcomes that is currently under-utilized.[13] Depression occurs in 5-58% of hospitalized adults, depending on how cases are defined.[14,15] Depression is often under-recognized and under-treated in acute care clinical settings,[16] and relatively few readmission prediction models incorporate mental health related symptoms.[17]

While several reviews have examined methods of screening for depression in hospitalized patients[14] or the effectiveness of screening in primary care,[18,19] to our knowledge no systematic review has examined the impact of depression on short-term prognosis after discharge from acute care. Therefore, the purpose of this systematic review was to summarize all studies that evaluate whether hospitalized patients with depression are at higher risk of 30-day all-cause readmission or all-cause mortality after being discharged from hospital.

## METHODS

This study followed an *a priori* protocol developed according to *PRISMA* criteria.[20]

**Data Sources and Search Methods**

We searched CINAHL, Ovid MEDLINE, Ovid EMBASE, and PsycINFO from inception to January 9, 2015 and the last 5 years of PUBMED for full publications with any of the following Medical Subject Headings: "Depressive Disorder", "Depression", "patient readmission", "Interviews, psychological", "inpatients" with restrictions for peer reviewed publication, humans, adults aged ≥18 years, and the English language. Search strategies were developed with a librarian (search terms and outputs are supplied in Online Supplement Figure e2.1). We manually searched reference lists of all included studies and relevant review articles and contacted content experts to identify additional publications.

**Eligibility Criteria and Selection of Studies**

Two authors (JP and LW) independently screened full texts of all relevant articles for inclusion. Disagreements were resolved by consensus or a third reviewer (SM). We considered any original research that compared readmission or mortality after discharge for hospitalized patients with versus without depression identified by any validated depression measure,[21] including any study design that incorporated at least 30-day follow-up post-discharge. We excluded studies that examined patients hospitalized in non-acute care settings or on surgical, psychiatric, obstetric, or intensive care services. We calculated Cohen's κ coefficient to evaluate inter-rater agreement on study selection.

**Data Extraction**

Data were abstracted by two authors (JP and LW). Disagreements were resolved by consensus or a third reviewer (SM). We contacted authors of all included studies to obtain missing data. If unavailable, crude data were estimated from published survival curves employing validated techniques in R (version 3.1.2) and *Digitizeit* (http://www.digitieit.de/).[22,23]

We sought information on trial characteristics (country, type of hospital, inclusion and exclusion criteria, sample size, follow-up duration, attrition); participants (age, sex, ethnicity, level of education and social support, comorbidities, marital status); exposure ascertainment (self-report depression screening tool or diagnostic interview for depression); and outcomes (primary: 30-day all-cause readmission or mortality, secondary: 90-day all-cause readmission or mortality, emergency department (ED) visits, primary care physician (PCP) visits).

**Data Synthesis and Statistical Analysis**

Where possible, we calculated pooled risk ratios (RR) with 95% confidence intervals (95%CI) using random-effects models in Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark, 2014). Heterogeneity was assessed using the Higgins $I^2$ statistic, with values of < 25%, 25-50%, and >50% representing low, moderate, and high heterogeneity.[24,25] Statistical significance was considered a two-sided p-value ≤0.05.

**Quality Assessment and Risk of Bias**

We assessed study quality using the 9-item Newcastle-Ottawa scale with 0-3, 4-6, and 7-9 stars considered low, moderate, and high quality, respectively.[26,27] Adjusted estimates in individual studies were examined to assess for confounding. We generated funnel plots in RevMan 5.3 and conducted Egger tests using STATA 13 (Statacorp LP, College Station, TX, USA, 2013) to assess for publication bias.[28]

**RESULTS**

**Study Selection**

After removing duplicates, we identified 4066 reports and reviewed 133 reports in full text (Figure 2.1). Despite our broad study inclusion criteria, we found only 35 longitudinal studies addressing this question. All 35 authors were contacted for outcome data and missing

information (response rate of 34%). We had to exclude 17 studies, as they did not collect outcomes within 90-days of discharge. Only 4 studies had published crude data for outcomes within 90-days,[29–32] but after contact with authors, we received unpublished data for a further 7 studies[33–39] (including individual level data for 2 cohorts).[38,39] We were able to estimate crude data from Kaplan-Meier curves for another 3 studies.[40–42] Another 4 studies did not collect the outcomes we were interested in individually. These studies were included in this systematic review but are not meta-analyzable in our models: three authors could only provide composite end point data[43–45] and one author provided unadjusted hazard ratios for which crude outcome data could not be retrieved.[46] Inter-reviewer agreement for inclusion was 80% (Cohen's $\kappa$=0.60).

**Characteristics of Included Studies (Table 2.1)**

The 18 studies ranged in size from 58 to 1418 patients; 13 were cohort studies and 5 included secondary analytic data from randomized control trials.[29,34,37,41,43] All studies ascertained depressive status by screening during index medical admission with either diagnostic interview or self-report questionnaires, although a variety of scales and definitions for depression were used (see Online Supplement, Table e2.1). Screening interviews were conducted mostly by research assistants or nurses (68%) or self-administered (21%). Most studies examined specific patient subgroups (10 cardiac, 3 pulmonary, and 2 elderly). Attrition rates for readmission and mortality data were low (average <1% among entire sample of studies). All studies scored at least 5 on the Newcastle-Ottawa scale– e Supplement Table e2.2 and were thus considered of at least moderate quality.

**Prevalence and Recognition of Depression**

The range of depression prevalence in hospitalized medical patients was 14% to 79%, with a median of 32% (interquartile range 27% to 40%, Table 2.1); in those studies that used a

diagnostic interview, the prevalence tended to be lower for major depression, with median of 17% (interquartile range 16% to 22%, Table 2.1). None of the included studies reported frequency of clinically recognized depression (i.e. prior to screening for the study). Only two studies assessed the persistence of depression after discharge: one reported that depression persisted in 53% (by screening questionnaire) and 34% (by diagnostic interview) of patients at 30-days,[45] while the other reported 48% persistence at 90-days after discharge according to a combined screening method.[44]

**Hospital Readmission**

Among patients discharged from acute care medical wards (4 studies reporting on 5 cohorts), 395 of 2433 (16.2%) patients were readmitted within 30-days (Figure 2.2). Hospitalized patients with depression were more likely to be readmitted within 30-days after discharge, 20.4% vs. 13.7% (RR 1.73, 95% CI 1.16-2.58, p=0.007; $I^2$=55%; Figure 2.2), compared to those without depression. Results were consistent for 90-day readmissions (39.8% vs. 31.0%, RR 1.68, 95%CI 1.13-2.50; $I^2$=76%, p=0.01; n=1543 patients, Online Supplement Figure e2.2) in 6 studies. One individual study examined short-term readmission within 6 months after discharge, but was not meta-analyzable in this model as it presented only hazard ratios and not raw data; however, it did report a 50% increased risk of readmission (adjusted hazard ratio 1.50, 95%CI 1.03-2.17).[46]

**All-Cause Mortality after discharge**

Among medical patients discharged from acute care in 9 studies, 69 of 3397 (2.0%) patients died within 30-days (Figure 3). Medical patients discharged with depression were more likely to die within 30-days, 2.8% vs. 1.5% (RR 2.13, 95% CI 1.31-3.44, p=0.002; $I^2$=0%; Figure 2.3), compared to those without depression. Similar results were found for 90-day mortality

(7.7% vs. 4.1%, RR 2.01, 95%CI 1.47-2.76; $I^2$=4%, p<0.001; n=3784 patients, Online Supplement Figure e2.3) in 11 studies.

**Emergency Department and Primary Care Physician Visits**

Four studies examined the use of emergency department (ED) or primary care physician (PCP) services within 90-days of discharge but 3 did not have extractable data for meta-analysis. All showed increased utilization of health services for depressed compared to non-depressed patients after discharge.[29,43–45] Depressed patients were more likely to visit the emergency department (adjusted IRR 1.73, 95% CI 1.27-2.36),[43] had significantly more medical encounters (e.g. PCP, ED visits, hospital admissions, laboratory tests, home care, mean 2.9 vs. 2.6, p=0.05)[45] and had a greater number of ED visits alone (27 vs. 15 per 100 patients, p=0.007)[29] within 30-days of hospital discharge compared to non-depressed patients. Similar results were found at 90-days.[43]

**Sensitivity and Subgroup Analyses**

Sensitivity analysis revealed no overall difference in pooled risk ratios or heterogeneity between M-H fixed-effects versus random-effects models or with addition of 0.5 to cells to permit inclusion of zero event data (Online Supplement Table e2.3). Although the subgroup comparisons were likely underpowered, there were no significant differences in the excess risk associated with depression whether studies used DSM-III or DSM-IV criteria, whether the study samples were disease specific or unselected general medical cohorts, whether studies were of moderate or high quality, or regardless of the severity of depression. There was no evidence of publication bias - funnel plots and Egger tests are reported online (Supplement, Figures e2.4 and e2.5, Table e2.3, respectively).

## DISCUSSION

### Summary of evidence

We found that depression was common in medical inpatients (about one third of all patients) and persisted for at least 30-days in up to half of those patients after discharge. We found strong evidence of an association between depression and poor short-term prognosis after discharge from hospital: a 73% excess risk of readmission and twice the risk of death within 30-days compared to those who reported no depression.

Our meta-analysis complements a recent narrative review that found concomitant depression to be a risk factor for poor prognosis among inpatients and outpatients with acute coronary syndrome[47] and another meta-analysis that demonstrated an increased risk of 2 year mortality among patients with depression after myocardial infarction.[48] To our knowledge, our study is the first to quantify the short-term post-discharge risks across a diverse group of medical inpatients.

The potential mechanisms underlying the observed relationship between depression and adverse patient outcomes after discharge are likely multiple. We believe there are two main possibilities. First, the excess risk associated with depression might be due to residual confounding, even though many of these studies did adjust for extensive lists of comorbidities,[29,31,33,34,36,37,40,42,43,46] including functional status,[46] social support[33] or anxiety.[42] This could occur if other risk factors were not sufficiently adjusted for, such as unrecognized comorbidities or concomitant disability, which are often present among chronically ill patients;[49] or if depression were a marker of psychosocial risk factors, such as stress,[50,51] anxiety,[52–54] poor resiliency,[55] or low social support.[56,57] Confounding could also occur if symptoms of acute illness inflate reports of somatic symptoms of depression on self-report questionnaires.[58,59]

Recent studies on the BDI, a widely used depression screening questionnaire, found that scores were higher in post-myocardial infarction patients when compared to outpatient controls[58] but with no differences between those groups in scores for the BDI-II,[60] a version with fewer somatic symptom questions.

Second, depression may cause adverse outcomes through indirect or direct pathways. Indirect causation could occur if depression hindered self-care behaviours, such as self-efficacy or medication adherence.[47,61] Depression could also act directly through pathophysiological changes. Some studies have suggested that depression is associated with metabolic abnormalities, including alterations in glucose transport[62] and increased vulnerability to obesity, type 2 diabetes mellitus, and/or diabetic complications - common conditions among hospitalized patients which also adversely affect post-discharge outcomes.[47,62]

**Strengths and Limitations**

This review has multiple strengths. By quantitatively synthesizing small observational studies of lower statistical power, we were able to detect a signal for an association between depression and short-term events post-discharge. We cast a broad search and included studies that examined a wide range of medical patient subgroups, thus increasing the generalizability of our findings. Further, we obtained unpublished data for 10 of the 18 relevant studies and present information that is otherwise unavailable in the literature.

There are also some limitations to our review. First, the included studies had heterogeneous screening measures and cut-offs; thus all cases of "depression" in these studies might not be equivalent. Many of the included studies assessed depression early during admission where psychological distress may be greatest. Most studies included patients with specific conditions like heart failure or chronic obstructive pulmonary disorder and not a wide

spectrum of medical inpatients. Moreover, few studies adjusted for psychosocial risk factors such as social support, anxiety, and functional status, and only two studies assessed the persistence of depression after discharge. Also, although the included studies were deemed to be of at least moderate quality, they could be at risk for sources of bias that may not be sufficiently appraised by the current version of the Newscastle-Ottawa scale for observational studies.[63] Although we excluded grey literature, we found no evidence of publication bias. Finally, as we did not have individual level patient data, we could not use meta-regression to explore sources of heterogeneity.

**CONCLUSIONS**

We have confirmed that depression is common, frequently persists after discharge, and is a marker for excess risk of readmission or death in hospitalized medical patients after discharge. Thus, depression is an additional marker that clinicians can use to identify patients at increased risk for suboptimal transition back to the community who may require additional resources after discharge. Moreover, although further research is required to evaluate whether treatment of individuals who screen positive for symptoms of depression but were not diagnosed with depression clinically can reduce 30-day readmission rates, our study does support calls for clinicians to routinely screen for depression in all medical patients prior to hospital discharge.

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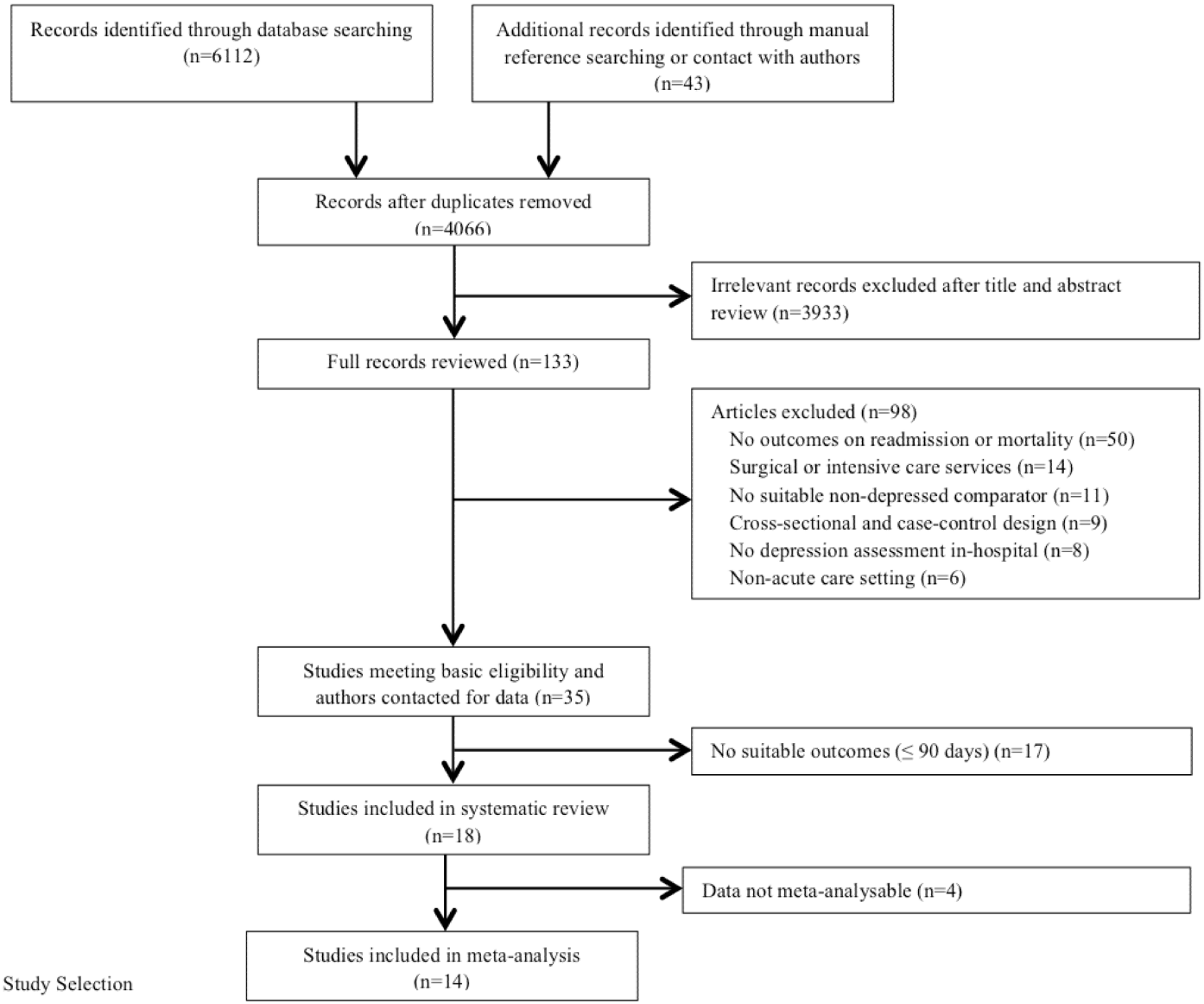



**Figure 2.1** Flow Diagram of Study Selection

**Figure 2.2** Risk Ratios for 30-day Readmission for Depressed Compared to Not Depressed Patients

| Study or Subgroup | Depressed Events | Depressed Total | Not Depressed Events | Not Depressed Total | Risk Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|
| Rumsfeld et al (37) | 37 | 138 | 96 | 482 | 1.35 [0.97, 1.87] | 2005 |
| Song et al (40) | 26 | 131 | 0 | 34 | 14.05 [0.88, 224.92] | 2009 |
| Papaioannou et al (36) | 10 | 91 | 3 | 139 | 5.09 [1.44, 18.00] | 2013 |
| Cancino et al (29) | 115 | 561 | 108 | 857 | 1.63 [1.28, 2.07] | 2014 |
| **Total (95% CI)** | | **921** | | **1512** | **1.73 [1.16, 2.58]** | |
| Total events | 188 | | 207 | | | |

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 6.65$, df = 3 (P = 0.08); $I^2 = 55\%$

Test for overall effect: Z = 2.69 (P = 0.007)

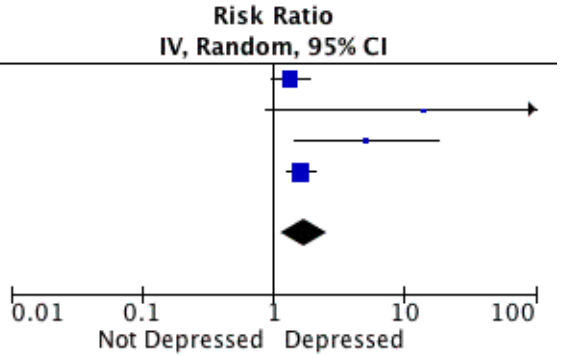


**Figure 2.3** Risk Ratios for 30-day Mortality for Depressed Compared to Not Depressed Patients

| Study or Subgroup | Depressed Events | Depressed Total | Not Depressed Events | Not Depressed Total | Risk Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|
| Frasure-Smith et al (33) | 1 | 68 | 0 | 150 | 6.57 [0.27, 159.13] | 1993 |
| Covinsky et al (41) | 12 | 197 | 15 | 376 | 1.53 [0.73, 3.20] | 1999 |
| Frasure-Smith et al (34) | 2 | 222 | 2 | 456 | 2.05 [0.29, 14.49] | 1999 |
| Lespérance et al (35) | 2 | 178 | 0 | 252 | 7.07 [0.34, 146.32] | 2000 |
| Almagro et al (38) | 2 | 43 | 1 | 87 | 4.05 [0.38, 43.39] | 2002 |
| Rumsfeld et al (37) | 9 | 142 | 10 | 491 | 3.11 [1.29, 7.51] | 2005 |
| Rollman et al (42) | 7 | 351 | 0 | 20 | 0.89 [0.05, 15.14] | 2012 |
| Almagro et al (39) | 0 | 55 | 1 | 79 | 0.48 [0.02, 11.48] | 2012 |
| Papaioannou et al (36) | 3 | 91 | 2 | 139 | 2.29 [0.39, 13.45] | 2013 |
| **Total (95% CI)** | | **1347** | | **2050** | **2.13 [1.31, 3.44]** | |
| Total events | 38 | | 31 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.07$, df = 8 (P = 0.85); $I^2 = 0\%$

Test for overall effect: Z = 3.07 (P = 0.002)

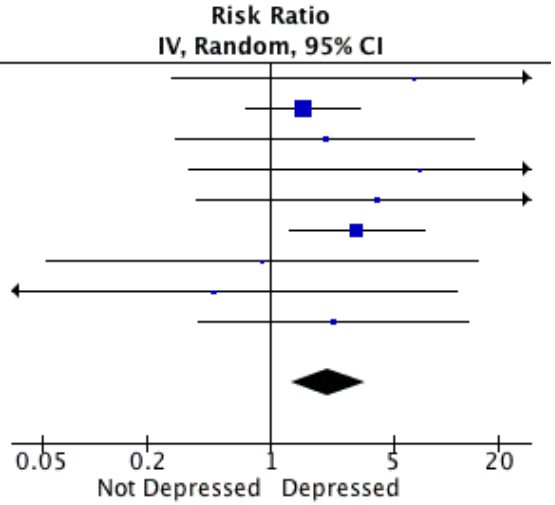


**Table 2.1** Summary of 18 longitudinal studies on post-discharge outcomes among depressive and non-depressed hospitalized patients

Studies that use a scale based on DSM-III criteria or a diagnostic interview according to DSM-III criteria

| Author, Date of Publication Enrolment period | Setting Country/Region No. hospitals | No. of inpatients Clinical features | Major exclusion criteria | Follow up months | Depression measure (cut-off) and screening method | Mean age (SD), years | % Female | Positive screen n (%) | Primary Outcome; Secondary Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Frasure-Smith et al,[33] 1993 1991-1992[c] | Canada/QC 1 urban teaching | 218 AMI | terminal noncardiac illness, unstable, not cognitive | 6 | BDI (≥10); mod. DIS by interviewer, after transfer to medicine | 60 (range 24-88) | 22 | 68 (31); 35 (16) | all-cause mortality |
| Frasure-Smith et al,[34] 1999 1991-1992[c] 1991-1994 | Canada/QC 1 urban teaching 10 urban area | 218; 678 AMI | terminal noncardiac illness, unstable, not cognitive | 12 | BDI (≥10) by interviewer, after transfer to medicine | 60 (11) | 32 | 290 (32) | cardiac mortality |
| Freedland et al,[32]1991 1990[e] | USA/MO 1 urban teaching | 58 CHF ≥ 75 yrs | dementia, medically unstable | 3 | modified DIS by psychiatric residents and interviewer | 78 (6) | 57 | 10 (17) | all-cause readmission; all-cause mortality |
| Fulop et al,[45] 2003 2002[e] | USA/NY 1 urban teaching | 203 CHF ≥ 65 yrs | – | 1, 6 | GDS (≥10); SCID-NP by interviewer, at discharge | 77 (8) | 53 | 73 (36); 44 (22) | depression; PCP, ED, care visits & readmission |
| Lespérance et al,[35] 2000 1994-1996 | Canada/QC 1 urban teaching | 430 unstable angina | terminal noncardiac illness, not cognitive, recent CABG | 12 | BDI (≥10); modified DIS by interviewer, 5 days after admission | 62 (11) | 29 | 178 (41); 120 (28) | cardiac death & MI; any death, angina readmission |
| Rumsfeld et al,[37] 2005 1999-2001 | CA, USA, UK multiple | 634 AMI with CHF | valvular or congenital heart failure | up to 32 | MOS-D (≥0.06) by interviewer, before discharge | 65 (11) | 28 | 143 (23) | all-cause death; CV death & readmission |
| Song et al,[40] 2009 2005-2005 | South Korea 2 urban teaching | 165 HF cardiology | if minor criteria for HF attributable to other medical condition | 6 | BDI (≥10) self-administer or interviewer 3-4 days of admin | 62 (13) | 49 | 131 (79) | HF readmission & all-cause mortality; HF readmit |

**Table 2.1** Summary of 18 longitudinal studies on post-discharge outcomes among depressive and non-depressed hospitalized patients (continued)

| Author, Date of Publication Enrolment period | Setting Country/Region No. hospitals | No. of inpatients Clinical features | Major exclusion criteria | Follow up months | Depression measure (cut-off) and screening method | Mean age (SD), years | % Female | Positive screen n (%) | Primary Outcome; Secondary Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Papaioannou et al,[36] 2013 2009-2010 | Greece/Athens 1 urban hospital | 230 AECOPD respiratory | other resp. illness, known depressed | mthly up to 12 | BDI-I (≥19) self-administer, 1st day | 71 (9) | 12 | 91 (40) | all-cause mortality; AECOPD readmission |
| Studies that use a scale based on or validated against DSM-IV criteria or a diagnostic interview according to DSM-IV criteria | | | | | | | | | |
| Almagro et al,[38] 2002 1996-1997 | Spain 1 urban teaching | 130 AECOPD medical | other pulmonary disease | Jul 1999 | GDS-SF (≥6) by interviewer, day before discharge | 72 (9) | 8 | 43 (33) | all-cause mortality |
| Almagro et al,[39] 2012 2003-2004 | Spain 1 urban teaching | 134 AECOPD medical | other pulmonary disease | 1[b], 36[a] | GDS-SF (≥6) by interviewer | 72 (10) | 5 | 55 (41) | all-cause mortality[a]; lung function[b], frailty[b] |
| Büla et al,[46] 2001 2000[e] | Switzerland 1 urban teaching | 401 medical ≥ 75 yrs | stay <24 hrs, elective/ facility transfer, unstable, not cognitive | 6 | GDS-SF (≥6) by interviewer, within 2 days of admission | 82 (75-99) | 61 | 90 (22) | all-cause readmission; all-cause mortality |
| Cancino et al,[29] 2014 2006-2007[c] 1 2008-2009 | USA/MA 1 urban tertiary | 680; 738 medical | nursing home or hospital transfer, isolated, suicidal | 1 | PHQ-9 ( (≥5) by interviewer, on admin | 50 (14) | 51 | 561 (40) | all-cause readmission; ED visits, PCP visits |
| Mitchell et al,[43] 2010 2006- 2007[c] | USA/MA 1 urban tertiary | 738 medical | nursing home or hospital transfer, isolated, suicidal | 1, 2, 3 | PHQ-9 (≥5) by interviewer, on admin | 50 (15) | 50 | 238 (32) | ED visits & all-cause readmission |
| Covinsky et al,[41] 1999 1990; 1990-1992 | USA/OH 1 urban teaching | 573 medical | ICU, oncology, telemetry, nursing home admissions | 36 | GDS-SF (≥6) by interviewer, within 2 days of admission | 80 | 68 | 197 (34) | all-cause mortality |

**Table 2.1** Summary of 18 longitudinal studies on post discharge outcomes among depressive and non-depressed hospitalized patients (continued)

| Author, Date of Publication Enrolment period | Setting Country/Region No. hospitals | No. of inpatients Clinical features | Major exclusion criteria | Follow up months | Depression measure (cut-off) and screening method | Mean age (SD), years | % Female | Positive screen n (%) | Primary Outcome Secondary Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Jiang et al,[30] 2001 1997- 1998 | USA/NC 1 urban teaching | 357; 331 (DIS only) CHF cardiology | suicidal, planned surgery, pregnant | 3, 12 | BDI (≥10) self-admin; mod DIS (+BDI only) by interviewer | 63 (13) | 33 | 126 (35); 46 (14) | all-cause mortality; all-cause readmission |
| Kartha et al,[31] 2007 2002- 2004 | USA/MA 1 urban safety-net | 144 medical recently hospitalized | planned readmission, unable to keep PCP appointments | 3 | PHQ-9 (algorithm) by interviewer | 55 (16) | 56 | 39 (27) | all-cause readmission |
| Koenig and Kuchbhatla,[44] 1999 1997[e] | USA/NC 1 urban teaching | 331 medical ≥ 60 yrs | stay <3 or >7 days, ICU/CCU, severe illness, nursing home transfers | 3, 6, 9, 12 | CES-D (≥16) or HAM-D (≥11) or DIS by psychiatrist, ≥ 3rd day | 70 (7) | 51 | 160 (48) | depression; physical disability, health visits & all-cause readmission |
| Rollman et al,[42] 2012 2007- 2009 | USA/PA 4 urban teaching | 471 CHF, suspected depressed | antidepressants users (excluded from - PHQ-2 group only) | up to 12 | PHQ-2; PHQ-9 (≥5 in +PHQ-2), by interviewer, ~ 4 day | 66 (13) | 35 | 371 (79); 351 (74) | all-cause mortality |

NOTE: Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; CHF, congestive heart failure; CV, cardiovascular disease; HF, heart failure; ICU/CCU, intensive care unit/coronary care unit; MDD, major depressive disorder.

Beck Depression Inventory (BDI); Medical Outcomes Study-Depression (MOS-D); Center for Epidemiologic Studies-Depression (CES-D); Geriatric Depression Scale (GDS) and short form (GDS-SF); Patient Health Questionnaire-9 criteria (PHQ-9) and short screen (PHQ-2); Hospital Anxiety and Depression Scale (HADS); Diagnostic Interview Schedule (DIS), modified for research interviewers (mod DIS); Structured Clinical Interview-Non Psychiatric Patient Version (SCID-NP).

[a]follow-up for mortality [b]follow-up for other specified outcomes

[c]subgroup of same cohort for those with identical enrollment periods

[d]BDI likely DSM III and DIS based on DSM IV

[e] Enrolment period not available. Period based on year of submission if specified or year previous to publication.

**eFigure 2.1**

**MEDLINE SEARCH STRATEGY**

1. exp Depressive Disorder/
2. Depression/
3. (depression or depressive).ti.
4. dysthym*.ti,ab.
5. or/1-4

6. patient readmission/
7. (rehospitalization or re-hospitalization or readmission or re-admission or mortality or (quality adj1 of adj1 life) or death or (depression adj5 prevalence) or (emergency adj3 visit*) or (prevalence adj5 depressive)).ti,ab.
8. 6 or 7

9. (inpatient* or in-patient* or (hospitali?ed adj2 patient*) or (acute adj1 care) or (hospital adj2 ward) or (hospital adj2 patient*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

10. (phq* or (health adj3 question*) or (geriat* adj3 depress* adj3 scale*) or GDS or (zung adj4 self* adj3 rat*) or (depress* adj3 inventor*) or whooley or (well* adj2 index) or (well* adj2 question*) or (CES-D adj3 scale*) or (hamilton adj3 depress*) or HAMD or (montgomery* adj3 depress*) or (cornell adj2 scale*) or goldberg or (beck* adj3 depress*) or BDI or BASDEC or (brief adj4 depression adj3 card*) or (quick adj2 inventor* adj3 depression adj2 symptom*) or QIDS-SR* or (computerized adj3 adaptive) or CAD-MDD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. (depress* adj10 (screen* or casefinding or case-finding or scale* or measure* or score* or instrument* or question* or inventor* or rating* or cards* or survey* or tool* or test* or interview* or exam*)).ti,ab.
12. Interviews, psychological/

13. or/10-12

14. (animals not humans).sh.

15. (comment or editorial or practice-guideline or letter or journal correspondence).pt.

16. exp Adult/
17. adolescent/ or exp child/
18. 17 not (17 and 16)

19. 14 or 15 or 18

20. ((depression or depressive) and in?patient*).ti.

21. 5 and 8 and 9 and 13

22. 20 or 21

23. 22 not 19

24. limit 23 to english

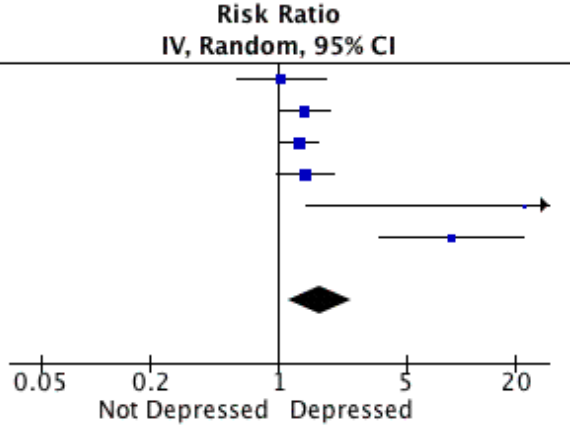
**2JUL2014**
**MEDLINE: 1576**
**+74 as of 9JAN2015**

**eFigure 2.2** Risk Ratios for 90-day Readmission for Depressed Compared to Not Depressed Patients

| Study or Subgroup | Depressed Events | Depressed Total | Not Depressed Events | Not Depressed Total | Risk Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|
| Freedland et al (32) | 6 | 10 | 28 | 48 | 1.03 [0.59, 1.80] | 1991 |
| Jiang et al (30) | 24 | 46 | 107 | 285 | 1.39 [1.01, 1.90] | 2001 |
| Rumsfeld et al (37) | 58 | 138 | 155 | 477 | 1.29 [1.02, 1.64] | 2005 |
| Kartha et al (31) | 22 | 39 | 42 | 105 | 1.41 [0.98, 2.03] | 2007 |
| Song et al (40) | 42 | 131 | 0 | 34 | 22.54 [1.42, 357.18] | 2009 |
| Papaioannou et al (36) | 29 | 91 | 5 | 139 | 8.86 [3.56, 22.04] | 2013 |
| **Total (95% CI)** | | **455** | | **1088** | **1.68 [1.13, 2.50]** | |
| Total events | 181 | | 337 | | | |

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 21.23$, df = 5 (P = 0.0007); $I^2 = 76\%$

Test for overall effect: Z = 2.58 (P = 0.010)

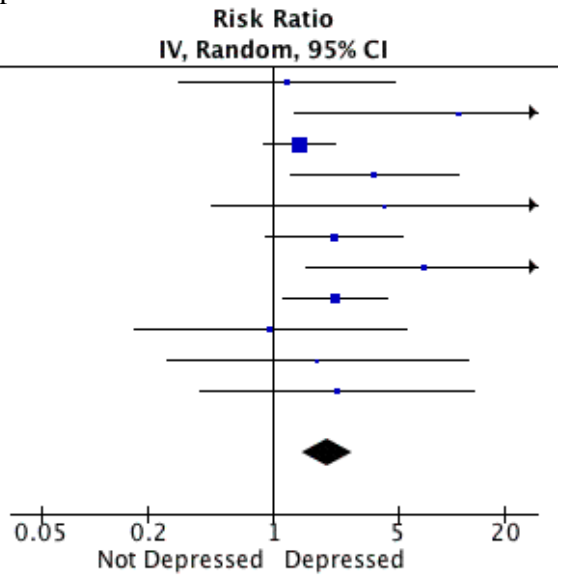


**eFigure 2.3** Risk Ratios for 90-day Mortality for Depressed Compared to Not Depressed Patients

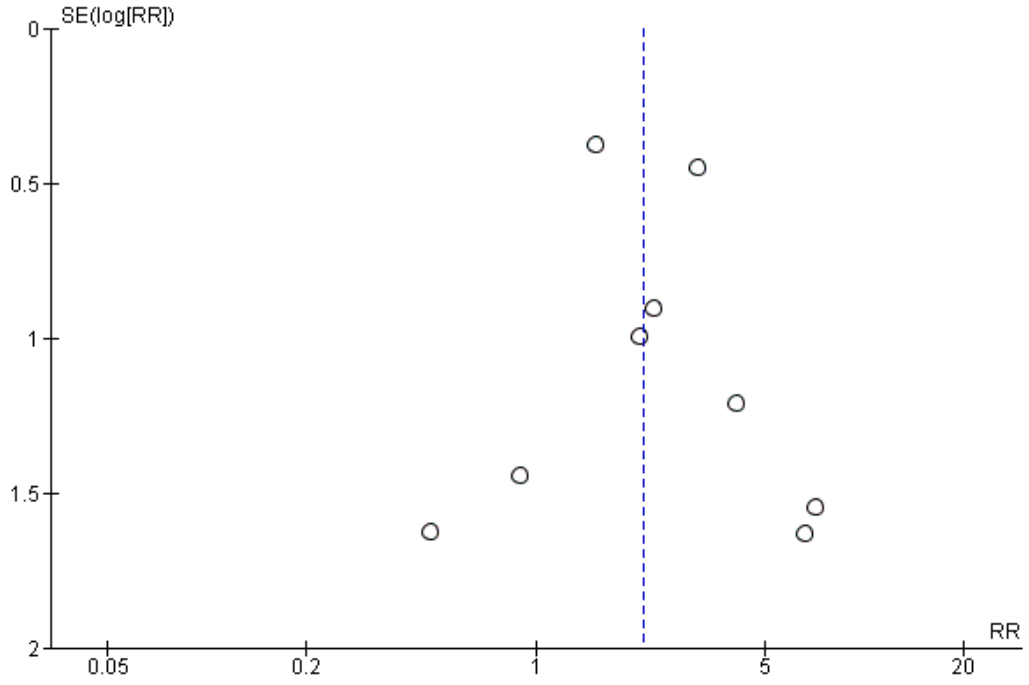
| Study or Subgroup | Depressed Events | Depressed Total | Not Depressed Events | Not Depressed Total | Risk Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|
| Freedland et al (32) | 2 | 10 | 8 | 48 | 1.20 [0.30, 4.83] | 1991 |
| Frasure-Smith et al (33) | 5 | 68 | 1 | 150 | 11.03 [1.31, 92.61] | 1993 |
| Covinsky et al (41) | 27 | 197 | 37 | 376 | 1.39 [0.87, 2.22] | 1999 |
| Frasure-Smith et al (34) | 9 | 222 | 5 | 456 | 3.70 [1.25, 10.90] | 1999 |
| Lespérance et al (35) | 3 | 178 | 1 | 252 | 4.25 [0.45, 40.50] | 2000 |
| Jiang et al (30) | 6 | 46 | 17 | 285 | 2.19 [0.91, 5.26] | 2001 |
| Almagro et al (38) | 7 | 43 | 2 | 87 | 7.08 [1.54, 32.65] | 2002 |
| Rumsfeld et al (37) | 13 | 142 | 20 | 489 | 2.24 [1.14, 4.39] | 2005 |
| Almagro et al (39) | 2 | 55 | 3 | 79 | 0.96 [0.17, 5.54] | 2012 |
| Rollman et al (42) | 31 | 351 | 1 | 20 | 1.77 [0.25, 12.29] | 2012 |
| Papaioannou et al (36) | 3 | 91 | 2 | 139 | 2.29 [0.39, 13.45] | 2013 |
| **Total (95% CI)** | | **1403** | | **2381** | **2.01 [1.47, 2.76]** | |
| Total events | 108 | | 97 | | | |

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 10.46$, df = 10 (P = 0.40); $I^2 = 4\%$

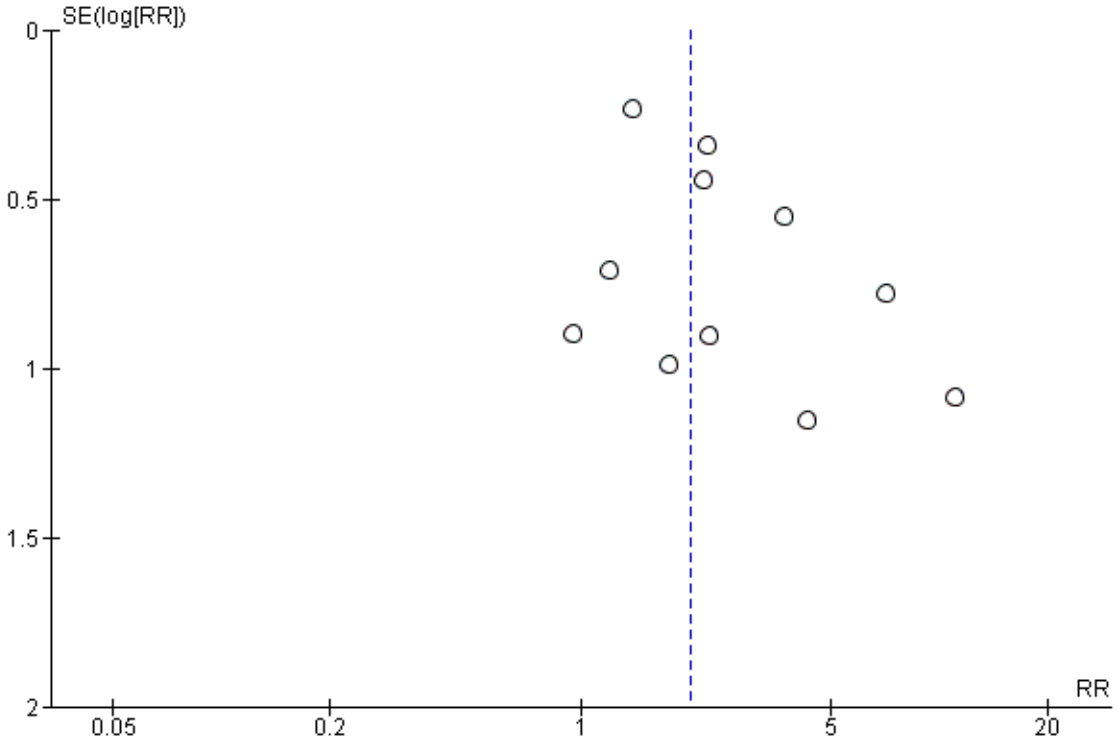
Test for overall effect: Z = 4.32 (P < 0.0001)



**eFigure 2.4** Funnel plot for 30-day Mortality



**eFigure 2.5** Funnel plot for 90-day Mortality



**eTable 2.1** Depression measures used among included studies

| **Depression Screening Scales** |
| --- |
| Beck Depression Inventory (BDI) |
| Medical Outcomes Study-Depression (MOS-D) |
| Center for Epidemiologic Studies-Depression (CES-D) |
| Geriatric Depression Scale (GDS) and short form (GDS-SF) |
| Patient Health Questionnaire-9 criteria (PHQ-9) and short screen (PHQ-2) |
| Hospital Anxiety and Depression Scale (HADS) |
| Hamilton Depression Rating Scale (HAM-D) |
| **Depression Diagnostic Interview** |
| Diagnostic Interview Schedule (DIS), modified for 'lay' interviewers (mod DIS) |
| Structured Clinical Interview-Non Psychiatric Patient Version (SCID-NP) |

**eTable 2.2** Newcastle-Ottawa Quality Assessment for Observational Studies

| Author and Date of Publication | Selection 'generalizability' | | | | Comparability | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Representative exposure group | Selection unexposed group | Exposure ascertainment exposure | Outcome not present at baseline | Comparable groups | Assessment of outcome | Adequate Follow up length? (yes ≥ 1 mth/no ≤ 1 mth) | Adequate follow-up | Score |
| Almagro et al,[38] 2002 | selected group | same | interview | yes | yes | self-report or record linkage | yes | LTFU ≤20%, | 7 |
| Almagro et al,[39] 2012 | selected group | same | interview | yes | yes | self-report or record linkage | yes | LTFU ≤20%, | 7 |
| Büla et al,[46] 2001 | somewhat | same | interview | yes | yes | self-report or PCP report | yes | LTFU ≤20%, | 8 |
| Cancino et al,[29] 2014 | somewhat | same | interview | yes | yes, yes | blind assessment, record linkage, and self-report | yes | LTFU ≤20%, | 9 |
| Mitchell et al,[43] 2010 | somewhat | same | interview | yes | yes, yes | blind assessment, record linkage, and self-report | yes | LTFU ≤20%, | 9 |
| Covinsky et al,[41] 1999 | somewhat | same | interview | yes | yes | record linkage | yes | complete | 9 |
| Jiang et al,[30] 2001 | somewhat | same | interview | yes | yes | self-report | yes | LTFU ≤20%, | 7 |
| Kartha et al,[31] 2007 | selected group | same | interview | yes | yes, yes | record linkage and self-report | yes | complete | 8 |
| Frasure-Smith et al,[33] 1993 | selected group | same | interview | yes | yes, yes | self-report, medical records | yes | complete | 7 |

**eTable 2.2** Newcastle-Ottawa Quality Assessment for Observational Studies (continued)

| Author and Date of Publication | Representative exposure group | Selection unexposed group | Exposure ascertainment exposure | Outcome not present at baseline | Comparable groups | Assessment of outcome | Adequate Follow up length? (yes ≥ 1 mth/no ≤ 1 mth) | Adequate follow-up | Score |
|---|---|---|---|---|---|---|---|---|---|
| Frasure-Smith et al,[34] 1999 | selected group | same | interview | yes | yes, yes | blind independent assessment, record review, and self-report | yes | complete | 9 |
| Lespérance et al,[35] 2000 | selected group | same | interview | yes | yes, yes | blind independent assessment, medical record, and self-report | yes | complete | 9 |
| Papaioannou et al,[36] 2013 | selected group | same | interview | yes | yes | blind assessment, self-report, hospital records | yes | LTFU ≤20%, | 7 |
| Song et al,[40] 2009 | selected group | same | interview | yes | yes | self-report, record review | yes | LTFU ≤20%, | 6 |
| Freedland et al,[32] 1991 | selected group | same | interview | yes | yes | self-report | yes | complete | 7 |
| Rollman et al,[42] 2012 | selected group | same | interview | yes | yes, yes | self-report, medical records | yes | complete | 7 |
| Rumsfeld et al,[37] 2005 | selected group | same | interview | yes | yes | blind independent assessment | yes | LTFU ≤20%, | 7 |
| Fulop et al,[45] 2003 | selected group | same | interview | yes | yes | self-report | yes | unclear | 5 |
| Koenig and Kuchbhatla et al,[44] 1999 | somewhat | same | interview | yes | yes | self-report | yes | LTFU >20%, | 6 |

**eTable 2.3** Sensitivity analyses, heterogeneity, and publication bias

| Analyses (n studies full; reduced) | Full M-H Fixed Effects Model | | | Exclusion of Zero-cell in M-H Fixed-effects Model | | | Full Random-effects Model | | | Exclusion of Zero-cell in Random-effects Model | | | Egger's Test |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RR | 95% CI | $I^2$ | RR | 95% CI | $I^2$ | RR | 95% CI | $I^2$ | RR | 95% CI | $I^2$ | a-intercept (90%CI), *P* |
| 30-day Readmission (4; 3) | 1.67 | 1.38-2.03 | 57 | 1.60 | 1.32-1.93 | 54 | 1.73 | 1.16-2.58 | 55 | 1.62 | 1.15-2.29 | 53 | na |
| 90-day Readmission (7; 6) | 1.66 | 1.41-1.95 | 80 | 1.54 | 1.31-1.80 | 79 | 1.68 | 1.13-2.50 | 76 | 1.58 | 1.09-2.29 | 77 | na |
| 30-day Mortality (9; 5) | 2.12 | 1.33-3.39 | 0 | 2.01 | 1.23-3.28 | 0 | 2.13 | 1.31-3.44 | 0 | 2.06 | 1.25-3.39 | 0 | 1.38 (-0.80-3.57) p=0.269 |
| 90-day Mortality (11) | 2.05 | 1.53-2.74 | 5 | na | na | na | 2.01 | 1.47-2.76 | 4 | na | na | na | 3.90 (0.39-7.40) p=0.072 |

# Chapter 3 Depression is associated with poorer short-term outcomes after discharge from medical wards: a multi-site prospective cohort study[1]

[1] *A version of this chapter has been submitted for publication.*

**ABSTRACT**

**Objective** Although death or readmission shortly after hospital discharge is frequent, predicting who is at higher risk is difficult. We evaluated whether in-hospital depression is associated with short-term readmission or mortality after discharge from medical wards.

**Design** Prospective cohort study of inpatients from 2 Canadian hospitals (7 medical wards).

**Data Sources** We assessed depression at discharge as defined as scores ≥11 on the 27-point Patient Health Questionnaire (PHQ-9). The primary outcome was all-cause readmission or mortality at 30-and 90-days post-discharge.

**Eligibility Criteria for Selecting Patients** Any non-institutionalized individual (i.e. admitted/discharged home) was eligible, except for those with severe cognitive impairment, communication barriers, or foreshortened life-expectancy (< 90-day follow-up).

**Results** Of 495 medical patients (median age 64 years, 51% women, top 3 admitting diagnoses heart failure [10%], pneumonia [10%], and COPD [8%]), 127 (26%) screened positive for depression at discharge. Compared with non-depressed patients, those with depression were more frequently readmitted or died: 27/127 (21%) vs. 58/368 (16%) within 30-days (adjusted odds ratio [aOR] 1.55, 95%CI 0.91-2.64, p=0.11, after adjustment for current prediction rules) and 46 (36%) vs. 91 (25%) within 90-days (aOR 2.00, 95%CI 1.25-3.17, p=0.004). Depression persisted in 40% of patients at 30-days and 17% at 90-days.

**Conclusions** Depression was common, under-recognized, and frequently persisted after discharge in hospitalized medical patients. Depression was associated with increased risk of short-term readmission or mortality independent of current prediction rules, and may serve as a prognostic factor to aid risk stratification.

## INTRODUCTION

Short-term readmissions or early deaths after hospital discharge are common and costly, and are therefore receiving increased attention. Between 10% to 40% of patients discharged from hospital are readmitted within 30-days,[1–3] accounting for at least 11% of total hospitalization costs.[4] Medical patients account for over two-thirds of all 30-day readmissions, thus General Internal Medicine (GIM) wards are often the target for interventions to reduce readmission rates.[4]

While many interventions have been tried to improve discharge transitions and reduce adverse events after medical hospitalization, their effects have been inconsistent and surprisingly few interventions have improved patient outcomes.[5–7] Risk stratification may increase the effectiveness of post-discharge interventions by targeting those at highest risk, but current models of risk prediction are less than perfect and it is important to determine if there are other as yet unidentified or novel risk factors.[8,10,9]

Depression may represent an under-recognized and potentially modifiable independent risk factor for unexpected readmission or early death. Depression is often poorly detected and under-treated in acute care settings,[10,11] is common in adults with chronic disease, and has been associated with worse long-term clinical outcomes.[12–15] Clinical symptoms of depression may range from dysthymia (mild persistent symptoms) to major depressive disorders (MDD). Although approximately 30-40% of hospitalized adults report some form of depression,[16,10] relatively few readmission risk prediction models include depression. Of 26 models to predict risk of hospital readmission,[9] only 5[17–21] specified a history of depression (based on claims data or chart review) and none captured depressive symptomatology at the time of discharge.

Therefore, we studied whether the presence of moderate-to-severe depression at the time of discharge independently predicts all-cause readmissions or early mortality after discharge in a representative cohort of internal medicine patients.

## METHODS

### Setting and Subjects

This study was conducted at two tertiary-care teaching facilities in Edmonton, Alberta, Canada (University of Alberta and Royal Alexandra hospitals). As discussed in full elsewhere,[22] we enrolled adult Albertans hospitalized on 7 General Internal Medicine (GIM) wards who were being discharged back to the community between October 2013 and November 2014. The Health Research Ethics Board at the University of Alberta approved all study procedures (project ID Pro00036880) and all patients provided written informed consent.

We excluded individuals with severe cognitive impairment (≥5 errors on the Short Portable Mental Status Questionnaire),[23] communication barriers (e.g. non-English speaking or aphasia), or foreshortened life-expectancy precluding 90-day follow-up.[22] Trained research assistants administered all baseline questionnaires and functional tests at the bedside within 48 hours prior to discharge and different research personnel (blinded to baseline assessments and with independent adjudication of events by medical experts) contacted patients at 30-days and 90-days post-discharge to collect outcomes data verified using provincial electronic medical records.

### Independent Variable of Interest (Depression)

Depression was assessed prior to discharge using the previously validated 27-point Patient Health Questionnaire (PHQ-9).[24] The PHQ-9 is a self-report measure based on the 9 diagnostic criteria for major depression in the DSM-IV. For our main analysis we used a cut-off score of 11 or greater which has been shown to optimize accuracy in the hospital setting (89% sensitivity and 89% specificity) for detection of depression.[25] Of note, hospital attending staff were informed if PHQ-9 scores ≥ 14 or patients reported suicidal ideation. We repeated the PHQ-9 in all patients 30-and 90-days after discharge and examined other cut-points for defining depression in sensitivity analyses.

### Outcomes

The primary outcome was all-cause readmission or mortality within 30-days and 90-days after discharge from the index hospitalization.

### Data Collection and Measurements

We collected a wide-range of socio-demographic and clinical factors at baseline. The LACE index was calculated for each patient. This is a validated scoring system commonly used to risk adjust the rate of 30-day readmission or death that includes length of hospital stay (L), acuity on index admission (A), Charlson Comorbidity Index (C), and number of emergency department visits during the 6 months prior to admission (E). The LACE index has been previously validated in both Canada and the US, in both general medical patients and populations with specific discharge diagnoses (e.g., heart failure), and it has reasonable accuracy with a c-statistic of about 0.7.[1,8,26]

**Statistical Analyses**

First, we compared patient characteristics and outcomes according to baseline depression status. We then sequentially fit multiple logistic regression models to predict the likelihood of readmission or mortality at 30-days and 90-days in patients with depression (PHQ-9≥11) compared to those without depression. Models were built "by hand" and potential confounders (based on literature review, clinical judgment, bivariate p-values <0.1, or greater than 10% changes in beta coefficients when included in models) were evaluated. The final parsimonious model adjusted for age, sex, and the LACE Index. To examine whether depression (PHQ-9≥11) improved model fit and provided any additional prognostic value, we used the c-statistic (equivalent to the area under the ROC curve), the Hosmer-Lemeshow goodness-of-fit test, and Integrated Discrimination Improvement (which quantifies how well patients with vs. without outcomes are separated with the addition of a single specified variable).[27] We undertook a series of sensitivity analyses to consider the PHQ-9 as a continuous covariate; to use other recommended PHQ-9 cut-points;[24,28] to examine the presence of a dose-response and to see if a history of depression (as identified by attending staff in the medical chart) could substitute for directly measured symptoms of depression. All analyses were done in STATA 13 (Statacorp LP, College Station, TX, USA, 2013). Statistical significance was considered a two-sided p-value ≤0.05. Based on *a priori* power calculations, we required 500 total patients and 125 depressed patients for 80% power to detect an OR ≥ 1.7, assuming a 15% event rate in non-depressed patients and 25% event rate in depressed patients (10% absolute difference).

## RESULTS

Primary outcomes data were collected for all 495 patients in our cohort at 30-days and 97% of these patients were accounted for at 90-days (Figure 3.1). Overall, the median age was 64 years [interquartile range [IQR] 51-78] and 51% were women); 115 (23%) had depression documented by the attending medical team in their chart (Table 3.1). The most common reasons for admission were heart failure (10%), pneumonia (10%), COPD (8%), urinary tract infection (5%), and acute diabetic complications (5%). The median Charlson Index score was 2 (IQR 1-4) and the median length of stay in hospital was 5 days (IQR 4-9).

### Prevalence and Correlates of Depression

The PHQ-9 identified 127 (26%) patients with scores ≥11 and of those, only 58 (46%) had depression noted in their charts. On the other hand, 57 (50%) of those with depression recorded in their charts had PHQ-9 scores < 11. In general, depressed and non-depressed patients were fairly comparable, although depressed patients were significantly younger, had higher anxiety scores, more problems with self-care, and reported lower rates of medication adherence (Table 3.1).

### Readmission or Mortality According to Depression

Overall, 85 (17%) patients were readmitted or died within 30-days and 137 (28%) patients within 90-days of discharge from hospital (Figure 3.2). Depressed patients were readmitted or died more frequently than non-depressed patients: 27 (21%) vs. 58 (16%) within 30-days (p=0.16) and 46 (36%) vs. 91 (25%) within 90-days after discharge (p=0.01) (Figure 3.2). In multivariable analysis adjusted for age, sex, and LACE score, depression was associated with an increased risk of readmission or mortality within 30-days (adjusted odds ratio [aOR]

1.55, 95%CI 0.91-2.64, p=0.11, c-statistic=0.69) and 90-days (aOR 2.00, 95%CI 1.25-3.17, p=0.004, c-statistic=0.71, Table 3.2, Table e3.1, Table e3.2). When the composite endpoint was disaggregated, it was evident that readmissions were driving results (Table 3.2).

**Post-Discharge Characteristics of Depression**

Depressed patients were more likely to have been prescribed antidepressants within 30-days (47% vs. 26%, p<0.001) and 90-days (53% vs. 25%, p<0.001) of discharge. Overall, of the 402 patients who completed the PHQ-9 at all three time points, 15% had scores of 11 or greater at 30-days and 9% at 90-days. Moderate-to-severe depression persisted in 40% of those initially depressed patients at 30-days and 17% at 90-days (Figure e3.1). Conversely, of the patients who were not depressed in-hospital (PHQ-9≤10), 7% were newly depressed at 30-days and 6% were newly depressed at 90-days (Figure e3.2).

**Sensitivity Analyses**

When we considered the PHQ-9 score as a continuous variable, it was only weakly correlated with readmission or mortality (at 30-days, Spearman's rho 0.08, p=0.08 and at 90-days, 0.13, p=0.004). When we then used the cut-point to define depression often used in outpatient primary care (PHQ-9≥10) rather than 11 as in our primary analysis, it provided similar results for readmission or mortality (aOR 1.43, 95%CI 0.85-2.39 at 30-days and aOR 2.12, 95%CI 1.35-3.32 at 90-days, Table e3.3). Finally, although PHQ-9 scores and history of depression were modestly correlated (Spearman's rho 0.34, p<0.001), depression recorded in the chart did not predict death or readmission at 30-days (aOR 0.80, 95%CI 0.44-1.46, p=0.47) or 90-days (aOR 1.05, 95%CI 0.64-1.72, p=0.84, Table e3.3).

## DISCUSSION

Moderate-to-severe depression was common in patients being discharged from internal medicine wards, but this was unrecognized by the attending team in more than half of affected patients. Symptoms persisted in 40% of patients at 30-days and 17% at 90-days. Moderate-to-severe depression at the time of discharge, but not a documented history of depression, predicted a nearly two-fold increased risk of short-term readmission or mortality independent of the best risk prediction tools currently available.

Our study confirms and extends the evidence regarding the prognostic impact of depression in general medical inpatients. In two analyses of relatively young medical inpatients, Mitchell *et al.* reported that PHQ-9 scores ≥5 were associated with a 73% greater risk of readmission or Emergency Department visits within 30-days after discharge,[29] while Cancino *et al*. reported a dose-response relationship with a 49% increase in readmissions within 30-days for those with mild (PHQ-9: 5-9) and 96% increase for those with moderate-to-severe (PHQ-9: 10-27) depression. [30] In a small study of 144 GIM patients, Kartha *et al*. found 3-fold higher readmission rate at 90-days in patients with major depression defined using a standardized PHQ-9 based scoring algorithm to diagnose major depression.[31] Furthermore, our study also extends the current evidence base in that we examined persistence of symptoms up to 90-days after discharge and adjusted for the previously validated LACE score at discharge in our multivariable analyses.

The potential mechanisms that link depression and adverse patients outcomes are likely multiple. First, depression could be connected to adverse outcomes through behavioural mechanisms if depression adversely affected self-care behaviours, such as adherence to diet,

medication, smoking cessation, or physical activity.[32–35] Second, underlying pathophysiological mechanisms could be responsible. For example, some studies have found elevated inflammatory markers (e.g. IL-6 and CRP cytokines) and cortisol in depressed patients,[34,36] and ongoing inflammation might have deleterious effects on patients recovering from heart failure, pneumonia, or COPD. Third, poorer prognosis could result from 'clinical inertia' wherein physicians may be less aggressive in their treatment prescriptions or dosing of even evidence-based medicine (e.g. statins) in patients with depression.[13,37]

Alternately, and in our opinion much less likely, our findings might be a result of residual confounding or bias. For example, if residual symptoms of acute illness conflated with self-reported somatic symptoms of depression – that is, if sicker patients were more likely to also report depressive symptoms and it was the former that was associated with increased risk of readmission or death rather than depression itself. To minimize this possibility, we chose to use a higher than conventional PHQ-9 cut-off score of 11 to define depression compared to the score of 10 recommended for primary care screening (a prior study reported that ongoing somatic symptoms minimally inflated PHQ-9 scores by approximately 1 point).[38] Moreover, we carefully collected information about addictions, functional status, and frailty and inclusion of these data did not materially affect the statistical significance or strength of association between depression and short-term adverse events in our study (Table e3.4).

**Limitations**

Although we prospectively screened all study participants, carefully collected serial data on depression and a number of other potential confounders, and conducted rigorous and blinded outcome ascertainment with independent adjudication, there are some limitations to our study.

First, we excluded patients from non-teaching hospitals and excluded non-medical admissions. Though this could limit generalizability, our final cohort included patients with a wide range of acute and comorbid conditions, varying age (20-98 years), and our top 3 most responsible admitting diagnoses are consistent with reports from other jurisdictions in Canada and the US.[4,8,3] Second, we excluded some very high-risk patients from our study (i.e., patients from long-term care, those with severe cognitive impairment, and those with foreshortened life expectancy) but we were more interested in detecting risk factors for readmissions amongst patients being discharged back to the community, which is the current focus of most efforts. Third, although we did not do psychiatric interviews to confirm depression diagnosis, we did use an easily deployed screening tool which has been previously validated and found to be accurate with a cut-off of 11 or more (sensitivity 89% and specificity 89% in a recent meta-analysis)[24,25].

**Conclusions**

We found that symptomatic depression was common for medical inpatients at the time of hospital discharge, that it was frequently unrecognized and remained symptomatic for months, and that it was an independent prognostic factor for readmission or mortality. Accordingly, current depression may be used to better identify and then target patients at particularly high risk of adverse events. Indeed, a review[5] of 46 interventions to reduce 30-day readmissions observed that the only effective discharge strategies were those that targeted high-risk groups. Furthermore, depression may actually be a modifiable risk factor for short-term readmission and mortality, but this would require a randomized trial to test. To our knowledge, there are no published trials of symptomatic depression treatment in hospitalized medical patients with the intent of reducing short-term readmission rates – and based on our study, there are many patients eligible for such a trial. In the meanwhile, we believe that our findings emphasize that all

clinicians who care for medical inpatients should consider screening patients for depression prior to hospital discharge.

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**Figure 3.1** Derivation of cohort

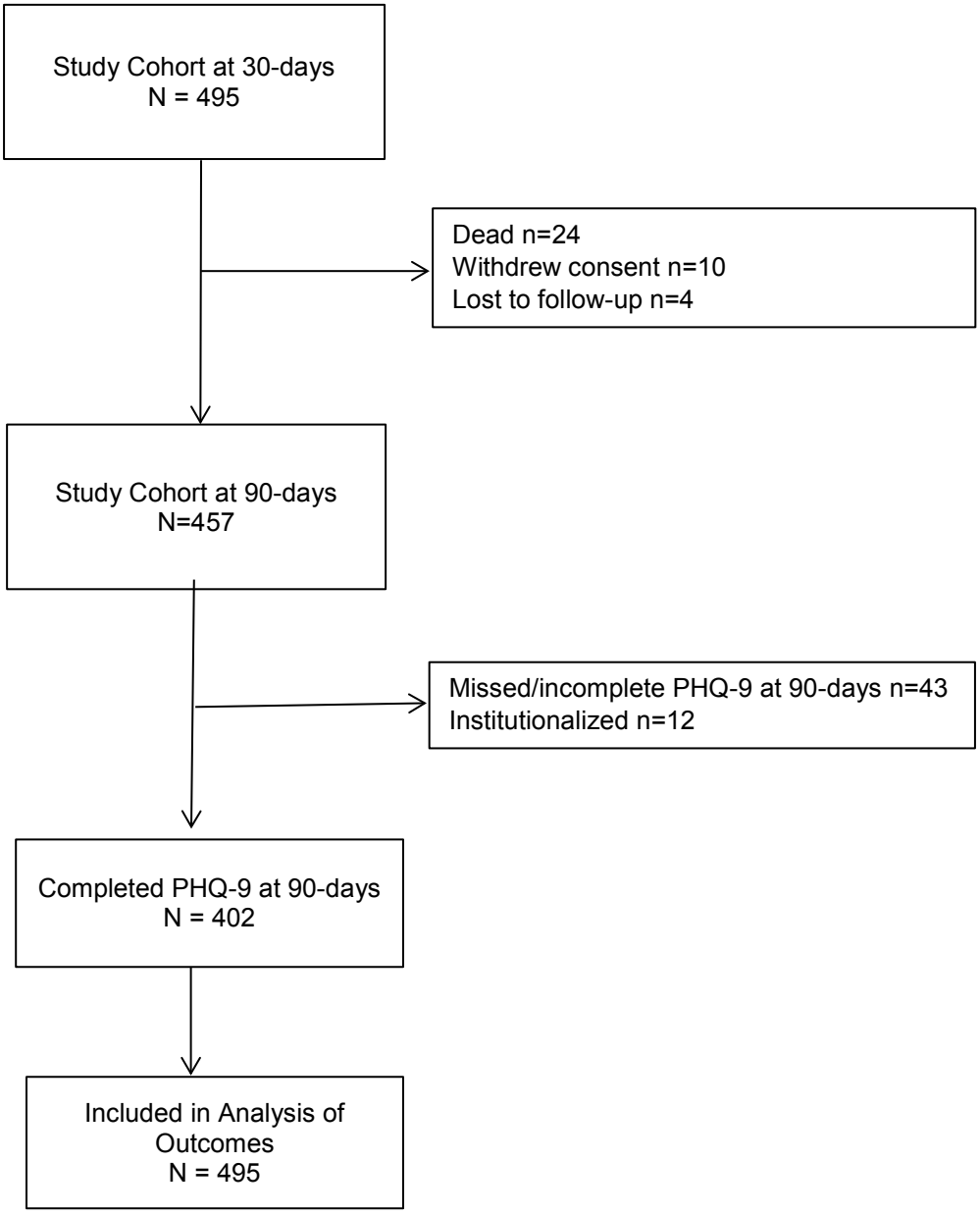
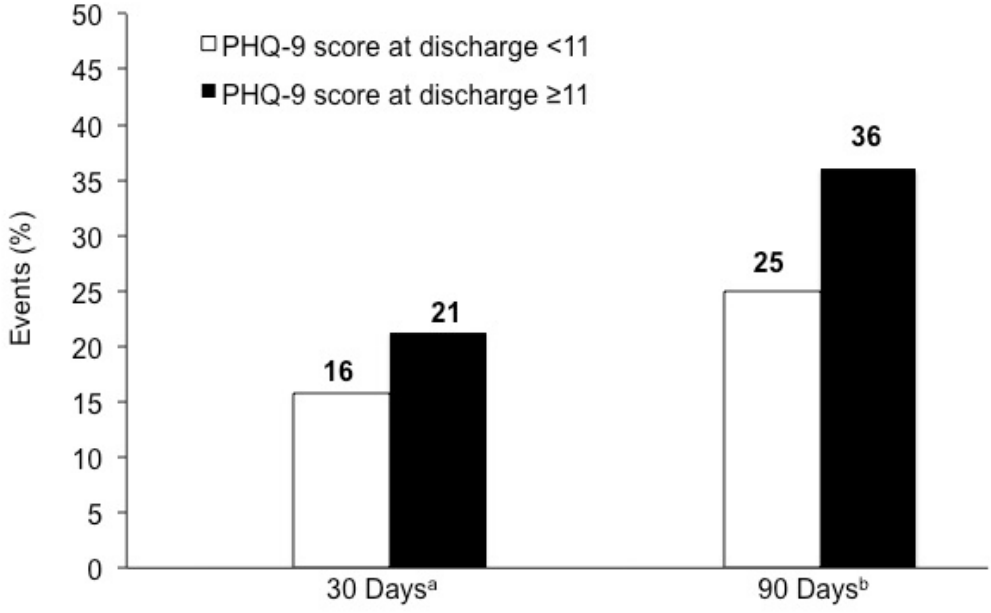


**Figure 3.2** Frequency of readmissions or death after discharge, according to PHQ-9 score




[a]Difference between groups adjusted for age, sex, and the LACE Index (p=0.11) [b](p=0.004).

**Table 3.1** Baseline Characteristics Stratified by PHQ-9 Score at Discharge

| | Depressed (PHQ-9≥11) | | Not Depressed (PHQ-9: 0-10) | | |
|---|---|---|---|---|---|
| | N=127 | % | N=368 | % | p-value |
| Age, years | | | | | |
| Mean, SD | 59.1 | 18.6 | 64.2 | 18.4 | <0.008 |
| Female | 71 | 56 | 179 | 49 | 0.16 |
| Divorced or Widowed | 33 | 26 | 64 | 17 | 0.02 |
| Reported "always" having social support for medical visits | 34 | 27 | 121 | 33 | 0.64 |
| Charlson Comorbidity Index | | | | | |
| Median, IQR | 2 | 1-4 | 3 | 1-4 | 0.07 |
| Mild cognitive impairment* | 86 | 68 | 287 | 78 | 0.016 |
| Depression noted on chart | 58 | 46 | 57 | 16 | <0.001 |
| Anxiety GAD-2 score | | | | | |
| Mean, SD | 3.2 | 1.9 | 1.1 | 1.4 | <0.001 |
| Alcohol addiction | 22 | 17 | 27 | 7 | 0.001 |
| Illicit drug addiction | 13 | 10 | 9 | 2 | <0.001 |
| Frail (Clinical Frailty Scale≥5)[22] | 46 | 36 | 116 | 32 | 0.33 |
| Reported no self-care problems(EQ-5D) | 78 | 61 | 276 | 75 | 0.01 |
| Reported missing any medication doses in past 2 weeks | 44 | 35 | 56 | 15 | <0.0001 |
| Number of prescription medications at discharge | | | | | |
| Mean, SD | 6.2 | 4.2 | 5.9 | 3.7 | 0.55 |
| Length of Stay | | | | | |
| Median, IQR | 5 | 4-8 | 5 | 2-9 | 0.22 |
| LACE Index | | | | | |
| Mean, SD | 11.5 | 2.9 | 11.6 | 2.9 | 0.62 |

*Scored from 3 to 4 errors on the Short Portable Mental Status Questionnaire).[22]

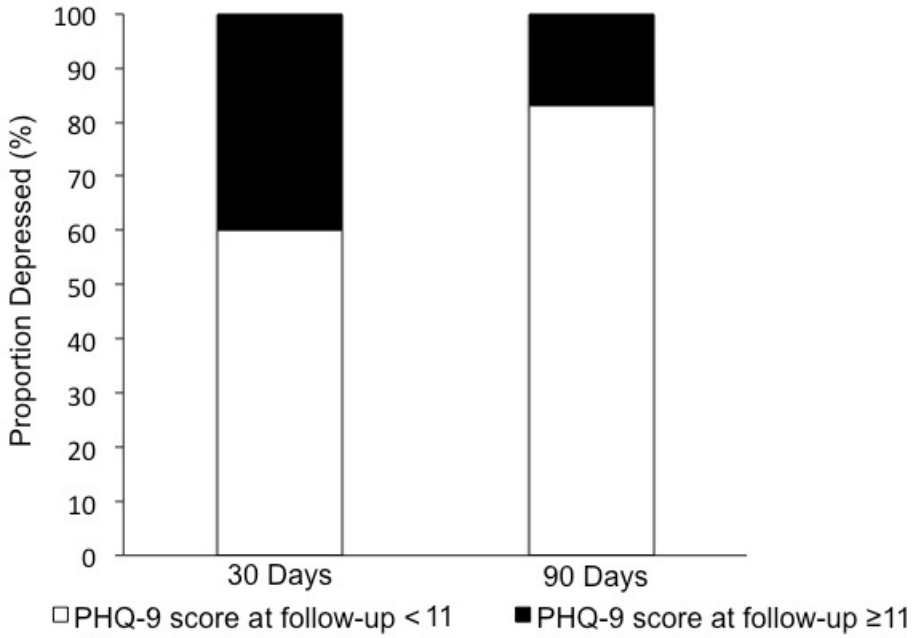
**Table 3.2** Association Between PHQ-9 Score at Discharge and Short-Term Outcomes

| | Depressed (PHQ≥11) | | Not Depressed (PHQ-9: 0-10) | | Multivariable Logistic Regression Estimates | | |
|---|---|---|---|---|---|---|---|
| | N=127 | % | N=368 | % | Adjusted Odds Ratio* | 95%CI | p-value |
| **30-days after discharge** | | | | | | | |
| Readmission or Mortality | 27 | 21 | 58 | 16 | 1.55 | 0.91-2.64 | 0.11 |
| Readmission | 26 | 20 | 55 | 15 | 1.54 | 0.90-2.64 | 0.12 |
| Mortality | 5 | 4 | 8 | 2 | 2.29 | 0.69-7.58 | 0.17 |
| **90-days after discharge** | | | | | | | |
| Readmission or Mortality | 46 | 36 | 91 | 25 | 2.00 | 1.25-3.17 | 0.004 |
| Readmission | 45 | 35 | 87 | 24 | 1.97 | 1.24-3.14 | 0.004 |
| Mortality | 10 | 8 | 14 | 4 | 2.97 | 1.20-7.34 | 0.02 |

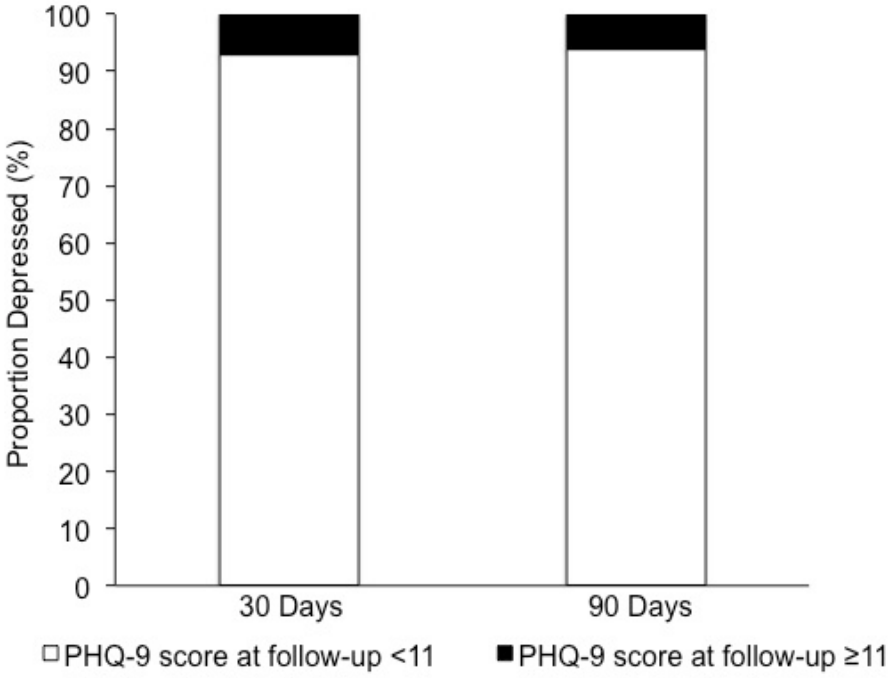
*Model adjusted for age, sex, and LACE. All c-statistics >0.7 and all p-values >0.4 for Hosmer-Lemeshow Goodness-of-fit Test.

## E-Appendix

**eFigure 3.1 Persistence of depression after hospital discharge**



**eFigure 3.2** Newly depressed patients after hospital discharge



**eTable 3.1** Full multivariable models for short-term outcomes

| | Readmission or Mortality | | | Readmission | | | Mortality | | |
|---|---|---|---|---|---|---|---|---|---|
| | aOR | 95%CI | p-value | aOR | 95%CI | p-value | aOR | 95%CI | p-value |
| **30-days after discharge** | | | | | | | | | |
| PHQ-9≥11 (ref<11) | 1.55 | 0.91-2.64 | 0.11 | 1.54 | 0.90-2.64 | 0.12 | 2.29 | 0.69-7.58 | 0.17 |
| Age | 1.00 | 0.99-1.02 | 0.97 | 1.00 | 0.98-1.01 | 0.68 | 1.02 | 0.98-1.06 | 0.43 |
| Sex, female | 0.91 | 0.56-1.48 | 0.69 | 0.97 | 0.59-1.58 | 0.89 | 0.74 | 0.23-2.39 | 0.61 |
| LACE | 1.26 | 1.15-1.378 | <0.001 | 1.26 | 1.14-1.38 | <0.001 | 1.60 | 1.25-2.05 | <0.001 |
| **90-days after discharge** | | | | | | | | | |
| PHQ-9≥11 (ref<11) | 2.00 | 1.25-3.17 | 0.004 | 1.97 | 1.24-3.14 | 0.004 | 2.97 | 1.20-7.34 | 0.018 |
| Age | 1.01 | 0.99-1.02 | 0.32 | 1.00 | 0.99-1.02 | 0.68 | 1.05 | 1.02-1.09 | 0.003 |
| Sex, female | 0.84 | 0.55-1.28 | 0.41 | 0.94 | 0.62-1.44 | 0.78 | 0.39 | 0.15-1.00 | 0.047 |
| LACE | 1.27 | 1.17-1.37 | <0.001 | 1.26 | 1.16-1.37 | <0.001 | 1.33 | 1.11-1.60 | <0.001 |

*aOR=adjusted odds ratio.

LACE is a validated predictive index that includes length of stay in hospital, acuity on index admission, Charlson Comorbidity Index, and emergency visits in the prior 6 months.[2]

**eTable e3.2** Measures of model performance

| | C-stat | Hosmer-Lemeshow | | C-stat | Hosmer-Lemeshow | | Discrimination | |
|---|---|---|---|---|---|---|---|---|
| | AUC | Chi2 | p-value | AUC | Chi2 | p-value | IDI | p-value |
| Models | Without Depression | | | With Depression | | | Difference in Model Slope | |
| **30-days after discharge** | | | | | | | | |
| Readmission or Mortality | 0.679 | 422.44 | 0.377 | 0.687 | 447.63 | 0.403 | 0.006 | 0.159 |
| Readmission | 0.673 | 418.50 | 0.429 | 0.683 | 442.02 | 0.451 | 0.005 | 0.188 |
| Mortality | 0.820 | 543.34 | <0.001 | 0.826 | 674 .01 | <0.001 | 0.015 | 0.279 |
| **90-days after discharge** | | | | | | | | |
| Readmission or Mortality | 0.689 | 418.35 | 0.431 | 0.705 | 444.60 | 0.443 | 0.016 | 0.015 |
| Readmission | 0.679 | 417.14 | 0.448 | 0.696 | 443.4 | 0.459 | 0.016 | 0.017 |
| Mortality | 0.817 | 338.55 | 0.997 | 0.835 | 380.96 | 0.982 | 0.029 | 0.069 |

*Models adjusted for age, sex, and the LACE Index.

**eTable 3.3** Sensitivity analysis of outcomes, according to alternative definitions of depression

| | Readmission or Mortality | | |
|---|---|---|---|
| | aOR | 95%CI | p-value |
| **30-days after discharge** | | | |
| Charted Depression | 0.80 | 0.44-1.46 | 0.47 |
| PHQ-9≥10 (ref<0-9) | 1.43 | 0.85-2.39 | 0.18 |
| Level of Severity PHQ-9 | | | |
| 0-4 | ref | - | - |
| 5-9 | 1.31 | 0.71-2.40 | 0.38 |
| 10-14 | 1.69 | 0.84-3.40 | 0.14 |
| 15-19 | 1.47 | 0.59-3.67 | 0.41 |
| 20-27 | 1.88 | 0.55-6.41 | 0.32 |
| **90-days after discharge** | | | |
| Charted Depression | 1.05 | 0.64-1.72 | 0.84 |
| PHQ-9≥10 (ref<0-9) | 2.12 | 1.35-3.32 | 0.001 |
| Level of Severity PHQ-9 | | | |
| 0-4 | ref | - | - |
| 5-9 | 1.32 | 0.78-2.23 | 0.31 |
| 10-14 | 2.72 | 1.49-4.96 | 0.001 |
| 15-19 | 2.26 | 1.05-4.89 | 0.038 |
| 20-27 | 1.63 | 0.53-5.04 | 0.34 |

*Models adjusted for age, sex, and the LACE Index.

**eTable 3.4** Sensitivity analysis of main effects model, with alternative covariates

| | Readmission or Mortality | | | | | |
|---|---|---|---|---|---|---|
| | | | | Additional covariate | | |
| | aOR | 95%CI | p-value | aOR | 95%CI | p-value |
| **30-days after discharge** | | | | | | |
| Main effects and frailty PHQ-9≥11[a] (ref<11) | 1.53 | 0.89-2.60 | 0.12 | 1.49 | 0.86-2.57 | 0.16 |
| Main effects and alcohol PHQ-9≥11[b] (ref<11) | 1.53 | 0.89-2.62 | 0.12 | 1.18 | 0.53-2.62 | 0.68 |
| Main effects and drug PHQ-9≥11[c] (ref<11) | 1.65 | 0.97-2.83 | 0.07 | 0.20 | 0.02-1.57 | 0.13 |
| **90-days after discharge** | | | | | | |
| Main effects and frailty PHQ-9≥11[a] (ref<11) | 1.95 | 1.22-3.11 | 0.005 | 1.41 | 0.88-2.28 | 0.16 |
| Main effects and alcohol PHQ-9≥11[b] (ref<11) | 1.89 | 1.18-3.02 | 0.008 | 1.74 | 0.88-3.44 | 0.11 |
| Main effects and drug PHQ-9≥11[c] (ref<11) | 1.92 | 1.20-3.07 | 0.006 | 1.78 | 0.66-4.82 | 0.25 |

*aOR=adjusted odds ratio.
[a] Model adjusted for frailty (CFS≥5)[22] in addition to age, sex, and the LACE Index.
[b] Model adjusted for charted alcohol addiction in addition to age, sex and the LACE Index.
[c] Model adjusted for charted drug addiction in addition to age, sex and the LACE Index.

## Chapter 4 General Discussion and Conclusions

Short-term hospital readmissions create substantial (and potentially avoidable) burdens on the healthcare system, patients, and their families. Frequently admitted and readmitted high-cost patients present with a myriad of potential prognostic characteristics that remain understudied and are yet very important for adequate discharge planning and targeted interventions. Symptoms of depression portend worse prognosis and are an under-recognized prognostic factor that may be potentially modifiable.

### *i. Summary of Findings*

The systematic review and meta-analysis conducted in **Project 1** demonstrated strong evidence of an association between depression and poorer short-term prognosis in medical patients discharged from hospital: a 73% excess risk of readmission within 30-days (RR 1.73, 95%CI 1.16-2.58) and a 68% excess risk of readmission within 90-days (RR 1.68, 95% CI 1.13-2.50) as well as twice the risk of death within 30-days (RR 2.13, 95%CI 1.31-3.44) and 90-days (RR 2.01, 95%CI 1.47-2.76), comparing depressed to non-depressed medical inpatients.

Results of the PROACTIVE cohort analysis in **Project 2** demonstrated that depression was common, affecting about 1 in every 3 medical inpatients, and that it frequently remained symptomatic after hospital discharge, with persistent symptoms in nearly half of patients after 1 month and 17% of patients after 3 months. Furthermore, the independent association between depression and adverse events was consistent with prior studies and showed a 55% increased adjusted risk of readmission or mortality within 30-days (aOR 1.55, 95%CI 0.91-2.64) and a 2-fold adjusted risk of readmission or mortality within 90-days (aOR 2.00, 95%CI 1.25-3.17) for depressed vs. non-depressed medical inpatients.

We provide 4 main advances to the evidence base regarding depression in hospitalized patients. First, our meta-analysis summarizes over 25 years of research, and to our knowledge, is the first to quantify the short-term post-discharge risks across a diverse group of medical inpatients. Second, we were able to identify low rates of clinical recognition of depression among inpatients. Third, we distinguished that current symptoms of depression, rather than just a reported history of depression, independently predict increased risk of adverse events shortly after discharge and provided additional prognostic information beyond the best currently available prediction rules. Last, we identified that depression at the time of discharge persisted for months after hospitalization in many patients.

Worse prognosis for chronic diseases in the presence of depression is well established and has been observed in many long-term studies.[1–8] Yet, few studies have been conducted to examine short-term events in general medical patients following hospital discharge. In secondary analyses of two randomized trials conducted in medical inpatients, Mitchell *et al.* reported that scores of 5 or higher on the PHQ-9 were associated with 73% higher risk of readmission or Emergency Department visits 30-days after hospital discharge;[9] Cancino *et al*. reported a dose-response relationship with 49% increased risk of 30-day readmission for those with mild depression (PHQ-9: 5-9) and 96% increased risk for those with moderate-to-severe depression (PHQ-9: 10-27),[10] and in a small cohort of 144 GIM patients, Kartha *et al*. observed 3-fold greater odds of being readmitted within 90-days for patients with major depression (as identified using a standardized algorithm based on PHQ-9).[11]

### *ii. Hypothesized mechanisms*

If our findings are not the result of chance, bias, or confounding, there are multiple potential mechanisms that could underlie the relationship between depression and worse

outcomes including behaviours, pathophysiological changes, and/or clinical inertia. Behavioural mechanisms may be responsible if depression hinders self-care behaviours, for instance, adherence to medication, diet, smoking cessation, and physical activity[12–15] or self-efficacy (i.e. perceived belief in one's capacity to successfully compete tasks).[16] Adherence may be a key-underlying pathway as non-adherence in patients portends poor prognosis after acute medical events,[14] with potential for sub-optimal adjustment to new medications, diet regimes, or specialist treatments often prescribed during hospitalization.

Depression may exert adverse effects through pathophysiological change. There is evidence of elevated inflammatory markers (e.g. IL-6 and CRP cytokines) and cortisol among depressed patients[14,17] and an association between depression and metabolic abnormalities, including alterations in glucose transport.[18] Ongoing inflammation might have deleterious effects on recovery from heart failure, pneumonia, or COPD, while metabolic abnormalities might increase vulnerability to obesity and diabetes or its' complications.[8,18]

Worse prognosis could result from 'clinical inertia' wherein physicians are less aggressive with treatment prescriptions or dosing of even evidence-based medicine (e.g. statins) in depressed patients.[19,20] This poses a treatment-risk paradox where those patients at highest-risk, such as with depression or functional limitations, are eligible yet receive less than expected treatments.[20]

### *iii. Alternate Explanations for Findings*

Though implausible given the preponderance of evidence, the poor prognosis associated with depression and short-term adverse events could result from chance, bias, or confounding. Bias might occur if symptoms of acute illness were conflated with reports of somatic complaints related to depression i.e. if sicker patients were more likely to also report depressive symptoms

and it was the former rather than depression itself that was associated with worse prognosis. Studies on the BDI-I, a widely used depression screening questionnaire, found higher depressive scores in post-myocardial infarction patients when compared to outpatient controls[21] but found for the BDI-II, an updated version with fewer somatic symptoms, very little difference between scores for post-MI patients and controls.[22] Minimal conflation has been found in the use of self-reported depression on the PHQ-9 in one study in which patients with systematic sclerosis scored approximately 1 point higher for somatic depressive symptoms compared to healthy controls.[23]

Alternately, residual confounding could occur if other risk factors, such as unrecognized comorbidity or concomitant disability, were not sufficiently adjusted for, even though many studies adjusted for extensive lists of comorbidities,[1,7,9–11,24–28] functional status,[28] or social support.[1] Moreover, in our analyses, data on prior alcohol or drug addiction, functional status, and frailty did not appreciably change the statistical significance or strength of association between depression and readmission or mortality (Table e3.4).

### *iv. Limitations*

Though our studies have multiple strengths, there are also are a few limitations. First, for the meta-analysis, we could not conduct a meta-regression to explore sources of heterogeneity, such as cut-off scores on depression scales or case definitions, as we did not have individual level patient data. Second, we excluded from our cohort some very high-risk patients (i.e. long-term care transfers and patients with severe cognitive impairment or foreshortened life expectancy), however the *a priori* interest was in patients discharged to the community. Third, while we did not conduct psychiatric interviews to confirm depression diagnoses, we did use a highly accurate and validated screening tool easily administered in a hospital setting.[29,30] Last, based on *a priori* power calculations, we were likely somewhat underpowered at 30-days as we

observed a 16% event rate in the non-depressed group and 21% event rate in the depressed group (only 5% absolute difference). A study of 500 total patients and 125 depressed patients has 80% power to detect an OR ≥ 1.7, assuming a 10% absolute difference in rates, and with an observed 25% event rate in the non-depressed and 36% event rate in the depressed group (11% absolute difference) at 90-days, we had more adequate power at in the 90-day analyses.

### *v. Implications for future research*

This body of work has at least two important clinical implications. First, the presence of symptomatic depression in hospitalized patients may better identify those patients at highest risk of adverse events who can then be targeted by interventions to improve post-discharge outcomes. A review of 46 trials to reduce 30-day readmissions found that only intervention strategies that risk-stratified and then targeted high-risk patients were effective.[31] Second, depression may be a modifiable risk factor for short-term readmission and mortality, but this should be tested in randomized trials. Moreover, our work underscores a necessity for more evidence to identify and confirm mechanisms through which depression may adversely affect outcomes, whether it be through behavioural mechanisms, such as medication non-adherence, or pathophysiologic mechanisms, such as unchecked inflammation.

### *vi. Direct Impact*

We believe the findings of our research highlight a need for all clinicians who care for medical inpatients to use validated tools to screen their patients for symptomatic depression prior to hospital discharge – this information is simply too clinically valuable to ignore anymore.

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