

Major Depression Associated With Rates of Cardiovascular Disease State Transitions

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The combined impact of depression and heart disease on worldwide morbidity and mortality is substantial. A recent World Health Organization report cited depression as the leading cause of disability worldwide.¹ Heart disease is the leading cause of death in North America and increasingly around the world. Numerous prior studies have identified an association between depression and cardiovascular disease.²⁻¹¹ These studies, however, have tended to focus on single aspects of the relationship, such as depression and hypertension or depression and coronary artery disease. Using claims data from a large health plan in Hawaii, this study takes a population-based approach and compares transition rates for patients with major depression with those for patients without major depression at several stages of cardiovascular disease progression.

METHODS

Study Population

The study population were members of the largest health insurance plan in Hawaii during the years 1999 to 2005. Members were eligible if they were aged 20 years and older and either free of hypertension, dyslipidemia, diabetes, coronary artery disease, and congestive heart failure, or if they met the eligibility requirements for specific analyses based on having 1 or more of these diseases. Patients included in the study also had sufficient continuous enrollment to contribute follow-up time for 1 or more of the analyses.

Study Variables

Age, sex, and enrollment information were taken from the insurer's enrollment files. Diseases were identified from submitted claims, and disease algorithms were based on those developed for disease management programs. The insurer's health plans had no prior authorization requirements for mental health diagnoses, including major depression, and claims could be submitted by both mental health professionals and non-mental-health physicians. Additionally, there was parity for the diagnosis of depression and, therefore, unlimited treatment benefits if medically necessary. Patients taking antidepressants were not assumed to have a diagnosis of depression. The disease algorithms were based on claims activ-

Objective: To compare patients with and without major depression with respect to their rates of transition to several stages of cardiovascular disease progression.

Study Design: Retrospective observational study.

Methods: The study used administrative data from a large insurer in Hawaii to evaluate associations of major depression with cardiovascular progression. Analyses used competing-risks models, models that allow more than 1 type of possible outcome event at the transition stages. All analyses were adjusted for age and sex.

Results: Among nearly 600,000 healthy members, those with major depression in the past year were 50% to 100% more likely than controls to develop hypertension or dyslipidemia. Rates were increased to a similar magnitude (1) among patients with hypertension or dyslipidemia who subsequently developed either the other condition or coronary artery disease and (2) among patients with hypertension and dyslipidemia who developed coronary artery disease or congestive heart failure. Transition rates to coronary artery disease or congestive heart failure also were increased 50% to 100% among patients with diabetes, hypertension, and dyslipidemia. The sequence of associations remained as strong examining depression 1-2 years in the past as with depression in the past year.

Conclusions: The results show a pattern of faster transitions for patients with major depression compared with patients without major depression across both the early and later stages of cardiovascular progression. Health plans offer a setting where patients with depression can be identified and where interventions might be undertaken to minimize the possible effects of depression on transition rates.

(*Am J Manag Care.* 2008;14(3):125-129)

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■ CLINICAL ■

ity during a year. To be categorized as having major depression, a patient needed to have 1 diagnosis of major depression in an inpatient setting or 2 diagnoses in an outpatient setting. Congestive heart failure and diabetes were identified by a combination of procedure and diagnosis codes in an outpatient setting. Patients were classified as having coronary artery disease if they had an acute myocardial infarction, a percutaneous coronary intervention, coronary artery bypass surgery, or ischemic vascular disease. Hypertension and dyslipidemia were defined by 2 or more diagnoses within a 12-month period, excluding those on radiology, laboratory, and pathology claims.

To study disease transitions, the algorithms were run by yearly intervals, but with quarterly increments such that each subsequent interval included the first 3 quarters of the preceding year and 1 additional quarter. The first yearly interval was calendar year 1999, the second extended from April 1999 to March 2000, the third from June 1999 to July 2000, and so on. Patients were assigned an initial disease state based on diseases identified in the yearly interval in which they were first continuously enrolled. Enrollment was based on Healthcare Effectiveness Data and Information Set criteria.¹² Disease transitions were assigned to the first quarter in which they were detected. As an example of the disease identification process, a patient might have hypertension and dyslipidemia in 1999, have no new diseases detected for the next 3 quarters, but then have diabetes detected in the fourth quarter. In the fourth quarter then, corresponding to the end quarter of the year 2000, the patient's disease state would be changed to

hypertension, dyslipidemia, and diabetes. Except for major depression, once a patient had evidence of a disease, the patient was considered to have the disease from that time onward. Major depression was not considered to be persistent. Patients were defined by quarters as having been depressed in either the past year or between 1 and 2 years ago.

Statistical Methods

The possible association of major depression with transitions to cardiovascular disease states was investigated by using competing-risks models.^{13,14} A competing risk arises when an individual can experience more than 1 type of event. In this study, the competing risks are for transitions from an initial disease state to a disease state with an additional comorbidity. The possible next comorbidities in the progressive sequence provided the competing risks. A small number of patients with more than 1 new disease identified in a follow-up quarter were excluded to simplify the analyses and the interpretation of the results. The competing-risk analyses were performed by using proportional hazard models with the Efron adjustment for ties.¹⁵ Results are expressed as relative rates of transition with 95% confidence intervals.

RESULTS

The number of patients in the 5 health states that were analyzed for disease transitions included nearly 600,000 initially healthy people; 80,000 to 90,000 members with hypertension, dyslipidemia, or both; and close to 40,000 patients with hypertension, dyslipidemia, and diabetes. The healthy patients averaged 48 years of age, whereas the age of patients with cardiovascular conditions ranged from the early fifties to the early sixties. For all of the health states, slightly more than half of the patients were female. Patients with major depression ranged by state from 4% to 7% per year; patients free of chronic disease had the lowest incidence of depression. Additional descriptive statistics can be found in the **Appendix Table** (available at www.ajmc.com).

The patients who were initially free of disease developed hypertension or dyslipidemia more rapidly if they had major depression in the

■ **Table 1.** Rate Ratios for Transitions Between Health States Among Patients With and Without Major Depression in the Past Year*

Starting State	Ending State	Rate Ratio (95% Confidence Interval)
Healthy	HTN	1.4 (1.3, 1.4)
Healthy	DYS	2.3 (2.2, 2.3)
HTN	HTN, DYS	1.5 (1.5, 1.6)
HTN	HTN, CAD	1.9 (1.5, 2.4)
DYS	HTN, DYS	1.6 (1.5, 1.7)
DYS	CAD, DYS	1.9 (1.5, 2.3)
HTN, DYS	HTN, CAD, DYS	1.8 (1.6, 2.1)
HTN, DYS	HTN, DYS, CHF	2.6 (2.1, 3.3)
HTN, DYS, DM	HTN, CAD, DYS, DM	2.2 (1.9, 2.6)
HTN, DYS, DM	HTN, DYS, CHF, DM	2.2 (1.7, 2.8)

*All analyses were adjusted for age and sex. HTN indicates hypertension; DYS, dyslipidemia; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus.

past year (Table 1). Further progression from hypertension or dyslipidemia to additional disease states also was associated with having major depression in the past year. Depressed patients with hypertension developed dyslipidemia 50% faster and coronary artery disease nearly twice as fast. Depressed patients with dyslipidemia developed hypertension 60% faster and coronary artery disease nearly twice as fast as patients without depression.

Further transitions from 2 or 3 diseases to 3 or 4 diseases followed a similar pattern (Table 1). Patients with depression in the past year had relative rates of transition that were about twice as fast as the rates for patients without depression. The relative rates of transition from hypertension and dyslipidemia to coronary artery disease and congestive heart failure were 1.8 and 2.6, respectively. The relative rates of transition for depressed patients from hypertension, dyslipidemia, and diabetes to coronary artery disease and congestive heart failure were about double the rates for patients without depression.

To further test whether depression in the past was associated with disease transitions, the analyses were repeated using major depression 1-2 years in the past (Table 2). The rates of transition in all analyses remained faster for patients with depression than for those without depression. The relative rates ranged from 1.5 to 2.5, a range comparable to the results observed when examining depression in the past year.

DISCUSSION

This retrospective observational study using health plan data demonstrates an association between major depression and rates of transition across several states of cardiovascular disease progression. Age- and sex-adjusted rates of hypertension or dyslipidemia were increased by 50% to 100% among nearly 600,000 initially healthy patients who had major depression in the past year. Rates were increased to a similar magnitude among patients with hypertension or dyslipidemia who subsequently developed both conditions, and among patients with hypertension and dyslipidemia who developed coronary artery disease or congestive heart failure. Transition rates to coronary disease or congestive heart failure also were increased 50% to 100% among patients with diabetes, hyper-

Table 2. Rate Ratios for Transitions Between Health States Among Patients With and Without Major Depression in the Past 1-2 Years*

Starting State	Ending State	Rate Ratio (95% Confidence Interval)
Healthy	HTN	1.8 (1.7, 1.9)
Healthy	DYS	2.6 (2.5, 2.7)
HTN	HTN, DYS	1.6 (1.5, 1.8)
HTN	HTN, CAD	1.9 (1.4, 2.5)
DYS	HTN, DYS	1.5 (1.4, 1.6)
DYS	CAD, DYS	1.5 (1.1, 2.1)
HTN, DYS	HTN, CAD, DYS	1.7 (1.4, 2.1)
HTN, DYS	HTN, DYS, CHF	2.5 (1.8, 3.3)
HTN, DYS, DM	HTN, CAD, DYS, DM	2.1 (1.7, 2.6)
HTN, DYS, DM	HTN, DYS, CHF, DM	2.1 (1.5, 3.0)

*All analyses were adjusted for age and sex. HTN indicates hypertension; DYS, dyslipidemia; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus.

tension, and dyslipidemia. Associations remained as strong with depression identified 1-2 years in the past as with depression diagnosed in the past year.

The links we found between depression and stages of cardiovascular progression are consistent with published research studies. Several epidemiologic studies, for example, have examined associations between measures of mental health and the subsequent development of hypertension.¹⁶⁻¹⁸ The relation between depression and hypertension may be explained biologically by the increased adrenergic activity in depression¹⁹⁻²¹ that may have a pressor effect on the cardiovascular system.²⁰ The excessive activation of the sympathetic nervous system associated with depression^{22,23} is believed to be one of the processes involved in the pathogenesis of heart failure.²⁴

Recent studies have examined associations between depression and the metabolic syndrome, a syndrome that includes serum triglyceride and cholesterol levels. Depressive symptoms were significantly associated cross-sectionally in adult,^{25,26} middle-aged,²⁷ and older populations.²⁸ Studies also report positive associations between depression and cortisol levels, levels that may increase with depression and adversely affect components of the metabolic syndrome.^{29,30} A study of older adults reported odds of 1.84 for depressed patients in the upper tertile for urinary cortisol levels compared with patients without depression and with lower cortisol levels.²⁸ The odds comparing all depressed patients with all patients without depression were 1.2. Beyond possible biologic effects, depression may lead to poor health habits that increase the risk of the metabolic syndrome.³¹ Reverse causation also may affect

Take-away Points

We compared the rates of transition of patients with major depression to those without across several stages of cardiovascular progression. The population was drawn from members of a large insurer in Hawaii.

- The results show a pattern of faster transitions for patients with major depression compared with patients without major depression across both the early and later stages of cardiovascular progression.
- Health plans offer a setting where patients with depression can be identified and where interventions might be undertaken to minimize the possible effects of depression on transition rates.

observed associations; obesity, for instance, might contribute to depression.

Several reviews and meta-analyses have evaluated the evidence that depression is a risk factor for coronary artery disease. In a review in 1998, Glassman and Shapiro concluded that published studies supported an association independent of smoking behavior, a behavior linked to depression.¹¹ Wulsin and Singal reviewed published studies in 2003 and concluded that depression was associated with coronary artery disease with a pooled risk from available studies of 1.64.³² Lett et al more recently reviewed published studies and concluded depression confers an increased risk between 1.5 and 2.0 for incident events among healthy individuals.⁶ Plausible etiologic mechanisms discussed included behavioral and lifestyle mechanisms, platelet activity, inflammation, and alterations in autonomic nervous system and hypothalamic pituitary adrenal function. In a 2006 review Nicholson et al cautioned, however, that depression is not yet established as a risk factor for coronary heart disease.³ Incomplete adjustment for potentially confounding factors in published studies leaves open the question of whether depression confers a risk independent of known risk factors. The pooled relative risk from 21 etiologic studies was 1.81.

This study is the first to our knowledge to examine the association between depression and the progression of cardiovascular disease for an entire health plan membership. Health plans offer a setting where identification of depressed patients might be linked to intervention programs where the depression can be appropriately managed. Health plan data, however, are limited in a variety of ways. Information such as smoking status, body mass index, and physiologic measures are not routinely available. Prescription data are limited to billed medications; free samples are not recorded, and adherence to free samples is unknown. The measures of depression were limited to the past 1 or 2 years; these may only serve as markers for more long-term etiologic processes. Another limitation is that morbidities such as depression and cardiovascular disease are limited to clinically managed states. Asymptomatic

risk factors and diseases may not be identified. An additional limitation is that the severity of disease often cannot be determined from claims data. The prevalence of depression likely will be underestimated from administrative data, although the prevalence estimates in our study, which ranged from 4.4% for healthy patients to 6.7% for patients with dyslipidemia alone, are consistent with results from community surveys.^{33,34}

Despite the inherent limitations in administrative data, we believe our study provides support for the strong and consistent association between depression and cardiovascular state transitions in an insured population. Further study is needed to examine whether adequately treating depression minimizes the possible impact on transition rates, and to determine what type of interventions or treatment protocols might be beneficial.

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Author Disclosure: The following authors (JD, RYF, DTJ, KAH) are employees of the Hawaii Medical Service Association, the insurer that provided the data used in this study. The Hawaii Medical Service Association also has disease management programs for the diseases discussed in this article. The other author (JKA) reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (JD, RYF, DTJ, KAH); acquisition of data (JD); analysis and interpretation of data (JD, DTJ, JKA); drafting of the manuscript (JD, RYF, DTJ, KAH); critical revision of the manuscript for important intellectual content (JD, RYF, DTJ, KAH, JKA); statistical analysis (JD); provision of study materials or patients (JKA); and administrative, technical, or logistic support (KAH).

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