Epidemiology

Depression leads to incident vascular disease: evidence for the relevance to primary care

Jeffrey F Scherrer*, Joanne Salas, Jay A Brieler, Bobbi J Miller, Dixie Meyer and F David Schneider

Department of Family and Community Medicine, Saint Louis University School of Medicine, St. Louis, MO 63104, USA

*Correspondence to Jeffrey F. Scherrer, Division of Research, Department of Family and Community Medicine, Saint Louis University School of Medicine, 1402 South Grand, St. Louis, MO 63104, USA; E-mail: scherrjf@slu.edu

Abstract

Background. Depression is a known risk factor for vascular disease in community cohorts and in large, system-wide, health care databases. It is not known if the association between depression and incident vascular disease exists when patient data is restricted to depression presenting in primary care.

Methods. Data were from a medical record registry capturing all primary care encounters at a large academic medical practice from 2008 to 2013. From 27,225 registry patients, we identified 7,383 patients free of vascular disease for 18 months prior to baseline. ICD-9-CM codes were used to define depression and vascular disease. Volume of health care use, demographics and comorbid diagnoses were obtained from the patient data registry. Cox proportional hazard models with time dependent covariates were computed to measure the association between depression and incident vascular disease before and after adjusting for covariates.

Results. Of the 7,383 patients initially free of vascular disease, 14% were diagnosed with depression and 8.6% developed vascular disease. Incident vascular disease was significantly (P < 0.05) higher among patients with depression (12.7%) compared to those without depression (7.9%). In the unadjusted model, depression was associated with a 49% increased risk of developing vascular disease (odds ratio [OR] = 1.49; 95% confidence interval [CI]: 1.19–1.86) and this association remained significant after adjusting for all potential confounders (OR = 1.28; 95% CI: 1.02–1.62).

Conclusions. The association between depression and incident vascular disease is observed in patients diagnosed and managed by primary care physicians. Primary care physicians have an opportunity to impact this association. Guidelines for primary care providers are needed to prompt aggressive depression treatment and vascular disease screening.

Keywords. Depression, heart disease, primary care, stroke, vascular disease.

Introduction

There is still debate about whether to officially designate depression as a cardiac risk factor. Major depression is now recognized by the American Heart Association as a risk factor for poor prognosis among patients with existing heart disease (1). This scientific statement should lead to changes in clinical practice such that cardiologists and primary care physicians routinely screen patients for depression. At this time, similar recommendations regarding depression as a risk factor for incident cardiovascular disease have yet to be published.

While most of the literature demonstrating the effect of depression on the course of existing heart disease has been done in patient cohorts, the seminal work demonstrating depression as a risk factor for new onset cardiovascular disease has primarily involved community samples (2–9). A common limitation of obtaining data from community samples is reliance on self-reported disease. In addition,
community-based cohorts are vulnerable to non-response and selection bias, such that participants tend to be of higher socioeconomic status and generally healthier than non-participants. In addition, very severely depressed and suicidal persons are excluded. Because of these sampling issues, community samples do not represent the real world measures and patients obtained from medical record data. A few exceptions to studies of depression and incident vascular disease in community samples have come from cohorts created using only medical record data (10,11). In such a patient cohort, Huang et al. (11), reported a 49% increased risk of coronary heart disease in patients with depression compared to those free of depression. In a large cohort of Veterans Administration (VA) patients, patients with depression, compared to those without, had a 39% increased risk of incident myocardial infarction and a 56% increased risk of heart failure (12). This risk remained even after adjusting for detection bias. These existing reports relied on medical record data obtained from any point of care, including psychiatry, and were not limited to patients in primary care clinics. Depression presenting in primary care, compared to psychiatry, is less severe (13) associated with fewer comorbid anxiety disorders (14) and less suicidal ideation (14). Because increasing severity of depression is accompanied with increasing risk of vascular disease (15–17), the previous risk estimates may not be applicable to patients with depression who are diagnosed and treated in primary care. While it is not definitive, there are several theories for the mechanisms behind the association of depression and incident vascular disease. Carney et al. (18) review postulates several mechanisms that may explain some of the association including common genetic vulnerability, lifestyle factors including smoking, cerebrovascular depression, non-adherence to medication, lower heart rate variability, greater platelet aggregation and last, inflammation. Thus epidemiological evidence paired with biological plausibility should prompt efforts to treat depression as a vascular disease risk factor.

However, practice guidelines have yet to establish depression as a risk factor for incident vascular disease (19). Determining if depression, as it presents in the primary care setting, leads to vascular disease will help establish if the general internal medicine (GIM) and family medicine (FM) physician have a role in reducing the risk of vascular disease in patients with depression. In the present study, we utilized medical record data from a cohort of patients who received care in FM or GIM to determine if depression in primary care settings is a risk for incident vascular disease.

**Methods**

**Subjects**
Clinical data were obtained from 27,225 patients of the Department of Family and Community Medicine’s Primary Care Patient Data Registry (PCPD). The PCPD Registry was developed by extracting electronic medical record data from clinics staffed by FM and GIM providers at a large academic medical health system located in the St. Louis, MO, metropolitan area. In 2013, a team of investigators, biostatisticians and informatics personnel developed a method of extracting raw files from our academic medical practice’s electronic medical record system, that is EPIC. Raw data was de-identified and variables created using information generated during patient visits. Useful information to create measures of disease and treatment are obtained from the PCPD’s ICD-9-CM codes, prescription orders, current procedure terminology (CPT) codes (a standard numeric coding scheme in the USA for describing medical procedures), social history, family history, demographics, laboratory orders, referrals and vital signs.

The Registry consists of all FM (n = 10,994) and GIM (n = 16,231) patients who had at least one encounter (e.g. office visit, procedure visit or clinical support) between 1 July 2008 and 31 July 2013. Encounters occurred in any of the ambulatory care sites located in the St. Louis metropolitan area. FM and GIM have separate clinics at each of the three locations for primary care which span the western suburbs, inner suburbs and central city in St. Louis. In total, ambulatory care sites are staffed by ~110 FM and GIM faculty and GIM residents and physician assistants. The creation of this retrospective cohort and its use for primary care research was approved by the Institutional Review Board.

**Measures**
All ICD-9-CM codes used to identify conditions were derived from diagnoses recorded during a clinical encounter.

**Exposure—depression**
Diagnoses were determined by the presence of ICD-9-CM codes at any time during the observation period. To be considered a case, the patient must have at least two occurrences of ICD codes indicating depression within a 12-month period. We have defined depression by this method in previous reports, citing evidence for the excellent agreement with patient reported depression and written medical record abstraction (10). Depression ICD-9 codes included 296.2, 296.3 and 311.

**Outcome measure—incident vascular disease**
We modeled a composite indicator of vascular disease because statistical power was inadequate when modeling the incidence of any specific vascular disease. Of the 633 composite incident vascular disease diagnoses 0.3% were a new diagnosis of hypertensive heart disease (ICD-9-CM: 402–405), 24.3% ischemic heart disease (ICD-9-CM: 412–414), 2.4% myocardial infarction (ICD-9-CM: 410–414), 58.1% other heart disease (ICD-9-CM: 420–429), 7.4% disease of pulmonary circulation (ICD-9-CM: 415–417) and/or 19.8% cerebrovascular disease (ICD-9-CM: 430–438).

**Covariates**
Covariates were selected if they were posited to be correlated with depression and vascular disease. Covariates included anxiety disorder unspecified, generalized anxiety disorder panic disorder, obsessive compulsive disorder, social phobia and posttraumatic stress disorders were defined by ICD-9 code and combined into a composite variable, any anxiety disorder. Any ICD-9-CM code for alcohol or drug abuse/dependence was modeled as substance use disorder. Traditional vascular disease risk factors included history of smoking obtained either through ICD-9-CM code or social history file. Hypertension, hyperlipidemia, type II diabetes mellitus were obtained from ICD-9-CM codes and obesity was defined by ICD-9-CM code or body mass index. To adjust for detection bias, we included a covariate measuring volume of health care utilization. The average number of clinic visits per month was calculated and the distribution divided into quartiles. We modeled a high utilization variable defined as the highest quartile of utilization versus all other levels of utilization. Demographic data available included age, race, gender and marital status.

**Analytic approach**
We used a retrospective cohort design with a 1-year washout period prior to baseline. Any patients with existing diagnosis of vascular disease during washout (1 July 2008 to 31 December 2009) were
excluded. This allows for computing the risk of incident vascular disease among patients who do versus do not have depression during the remaining observation period January 2010 to August 2013. Descriptive statistics were computed for bivariate associations between covariates and incident vascular disease using t-tests for continuous variables and chi-square tests for categorical variables. Hazard ratios for incident depression were estimated using Cox proportional hazards models. In survival models, depression, anxiety, hypertension, hyperlipidemia, type II diabetes mellitus and obesity were modeled as time dependent covariates that could occur anytime between baseline and incident vascular disease. History of smoking, demographics and health care utilization were time independent covariates. Month was the unit of follow-up time. Follow-up continued until onset of vascular disease or last date of available data (e.g. date of last clinical encounter). The Proc PHREG procedure in SAS version 9.3 (SAS Institute, Cary, NC) with α set at 0.05 was used for the Cox regression models. Two-tailed tests were conducted to allow for both risk factors and protective effects.

Eligibility criteria
From the base sample of 27225 patients, we required at least one visit in the washout period (1 July 2008 to 31 December 2009) and one follow-up visit after baseline (1 January 2010). Patients were eligible if they were older than 25 to allow for some risk of vascular disease. After applying these restrictions, 7492 subjects free of vascular disease at baseline remained. We then required a minimum of 12 weeks of follow-up time to allow for an opportunity for vascular disease to occur after depression. Subjects with vascular disease in the first month of follow-up or depression in the last month of observation were excluded resulting in a sample of 7464. Last, those with unknown race were excluded (n = 81) resulting in a final sample of 7383 patients free of vascular disease at baseline.

Results
During the observation period, 1003 patients were diagnosed as depressed. Depression was significantly associated with incident vascular disease (P < 0.01), with incident vascular disease almost twice as common among patients diagnosed with depression (12.7%) as compared to those without depression (7.9%). As shown in Table 1, patients diagnosed with depression were significantly older (P < 0.05) and disproportionately of white race (P < 0.01) and female (P < 0.01). Patients with depression were significantly less likely to be married (P < 0.01). All covariates were significantly (P < 0.01) more common among depressed versus non-depressed patients.

The distribution of patient characteristics by incident vascular disease is shown in Table 2. Patients with incident vascular disease, compared to those without, were significantly (P < 0.01) older and of minority race. Gender was evenly distributed by vascular disease status. Those with vascular disease were more likely to not be married (P < 0.01). Patients with vascular disease were also more likely have been diagnosed with depression (20% versus 13%, P < 0.01). Patients with and without vascular disease had an equal prevalence of any anxiety disorder (9.2%). Finally, those with vascular disease had a significantly (P < 0.01) higher prevalence of all remaining covariates compared to subjects without vascular disease.

Results of covariate adjusted Cox proportional survival models are shown in Table 3. In an age adjusted model, depression was significantly associated with risk of incident vascular disease (hazard ratio [HR] = 1.49; 95% confidence interval [CI]: 1.19–1.86). In a full model patients with depression, compared to those without, remained at significantly greater risk of incident vascular disease (odds ratio [OR] = 1.28; 95% CI: 1.02–1.62). In the full model, high health care utilization, hypertension, hyperlipidemia and diabetes remained significant risk factors for incident vascular disease (OR range: 1.26–1.61).

Conclusions
In a sample of over 7000 primary care patients, a diagnosis of depression was associated with a 28% increased risk of incident vascular disease after controlling for traditional cardiovascular and cerebrovascular disease risk factors including hypertension, hyperlipidemia and diabetes. The present findings are consistent with the growing number of studies of mood disorder and of incident vascular disease in patients selected to be free of vascular disease.
The lack of an association between anxiety disorders and vascular disease in adjusted models is also consistent with a previous report designed to determine if anxiety contributes to myocardial infarction when comorbid with depression (10). Findings from the current research coincide with two previous reports using large medical record cohorts that have demonstrated depression is an independent risk factor for vascular disease as measured by ICD-9-CM code (10,11). Despite different patient samples, the age adjusted hazard of vascular disease in the present cohort (HR = 1.49) was nearly the same as the estimate observed for the association between depression and incident myocardial infarction in a health care system wide sample of VA patients (HR = 1.39). This similarity in hazard ratios provides support for the validity of our variable definitions and methodological approach.

The present study advances the utility of medical record based research to test medical research hypotheses and more importantly demonstrates that the primary care setting provides an opportunity for expanding vascular disease risk evaluation to include depression. Hochman et al. (24) outlined a clinical intervention designed to reduce cardiovascular disease risk that incorporates emotional risk factors including depression, job stress and life events. This strategy, Prevention Oriented Primary Care-Abridged (POPCA), acknowledges traditional risk factors, but in the context of emotion and behaviour. The focus on primary care encounters, as well as the identified risk of vascular disease associated with depression in the current study, provides further support for widespread implementation of POPCA.

Depression is the fifth most common chronic disease managed by primary care physicians (25), and in a cohort limited to primary care, depression is a risk for vascular disease. Thus, the problem of physical consequences of depression should be addressed in this venue. The primary care physician has a crucial role in close monitoring of vascular health when diagnosing and managing patients with depression.


<table>
<thead>
<tr>
<th>Variable, no. (%)</th>
<th>No vascular disease (n = 6750)</th>
<th>Vascular disease (n = 633)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>51.5 (15.0)</td>
<td>63.5 (14.3)**</td>
</tr>
<tr>
<td>Non-white race</td>
<td>2615 (38.7)</td>
<td>297 (46.9)**</td>
</tr>
<tr>
<td>Male</td>
<td>2393 (35.3)</td>
<td>211 (33.3)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>3164 (46.9)</td>
<td>226 (35.7)**</td>
</tr>
<tr>
<td>Not married</td>
<td>3043 (45.1)</td>
<td>327 (51.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>543 (8.0)</td>
<td>80 (12.6)</td>
</tr>
<tr>
<td>Any depression</td>
<td>876 (13.0)</td>
<td>127 (20.0)**</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>619 (9.2)</td>
<td>58 (9.2)</td>
</tr>
<tr>
<td>Diabetes, type II</td>
<td>954 (14.1)</td>
<td>188 (29.7)**</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2227 (33.0)</td>
<td>365 (57.7)**</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2814 (41.7)</td>
<td>464 (73.3)**</td>
</tr>
<tr>
<td>Obese</td>
<td>3244 (48.1)</td>
<td>379 (59.9)**</td>
</tr>
<tr>
<td>Smoking history</td>
<td>2672 (39.6)</td>
<td>324 (51.2)**</td>
</tr>
<tr>
<td>Substante use/dependence</td>
<td>159 (2.4)</td>
<td>14 (2.2)</td>
</tr>
<tr>
<td>High utilization, top 25th percentile</td>
<td>1525 (22.6)</td>
<td>329 (52.0)**</td>
</tr>
</tbody>
</table>

* P < 0.05.
** P < 0.01.

Table 3. Adjusted associations between depression and risk of incident vascular disease in a cohort of primary care patients (n = 7383)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1—unadjusted a</th>
<th>Model 2—fully adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>1.49 (1.19–1.86)</td>
<td>1.28 (1.02–1.62)</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99–1.03)</td>
<td>1.01 (0.97–1.03)</td>
</tr>
<tr>
<td>Non-white race</td>
<td>1.01 (0.85–1.19)</td>
<td>1.04 (0.87–1.23)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.04 (0.87–1.23)</td>
<td>1.04 (0.87–1.23)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Not married</td>
<td>1.16 (0.97–1.40)</td>
<td>1.16 (0.97–1.40)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.25 (0.97–1.63)</td>
<td>1.25 (0.97–1.63)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>1.13 (0.96–1.33)</td>
<td>1.13 (0.96–1.33)</td>
</tr>
<tr>
<td>High utilization, top 25th percentile</td>
<td>1.61 (1.36–1.91)</td>
<td>1.61 (1.36–1.91)</td>
</tr>
<tr>
<td>Substante use/dependence</td>
<td>0.71 (0.56–1.38)</td>
<td>0.71 (0.56–1.38)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.54 (1.26–1.87)</td>
<td>1.54 (1.26–1.87)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.30 (1.10–1.54)</td>
<td>1.30 (1.10–1.54)</td>
</tr>
<tr>
<td>Diabetes, type II</td>
<td>1.26 (1.05–1.53)</td>
<td>1.26 (1.05–1.53)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.14 (0.97–1.35)</td>
<td>1.14 (0.97–1.35)</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>0.96 (0.69–1.34)</td>
<td>0.96 (0.69–1.34)</td>
</tr>
</tbody>
</table>

Bold text indicates significant HRs.

*All HRs and CIs calculated with Cox proportional hazards models.

aAn age-squared term was added to all adjusted models (Models 2–5).
Limitations
The patient cohort is limited to a large academic medical center and to the geographic region in the Midwest. Therefore generalizability to other regions of the United States and other countries is unknown. The primary care practices do not employ systematic screening for anxiety disorders, and vary in the degree of routine depression screening and training in behavioural health. This may have resulted in under-diagnosis of both conditions. Different levels of mis-classification bias may be present due to inter-physician variability in accurately diagnosing depression and given the additional behavioural health training of FM physicians, it may be that accuracy was greater among FM compared to GIM patients. A common limitation of medical record based cohorts, is the lack of important behavioural data such as exercise, diet, education and income. Additional research is needed to incorporate primary data collection to merge lifestyle measurements with medical record data.

Summary
In a primary care patient cohort, patients with depression had a significantly increased risk of incident vascular disease compared to those without depression. Patients with depression have a 28% increased risk of vascular disease which is similar to the risk of 26% we observed for diabetes. Clearly depression should be considered among the accepted risk factors for coronary heart disease and other forms of vascular disease. The American Heart Association’s 2014 Scientific Statement concluding depression is a risk for poor prognosis in patients with acute coronary syndrome has yet to be complemented with a statement that depression is associated with increased risk of developing cardiovascular and cerebrovascular disease. A similar scientific statement, that depression is a risk factor for incident vascular disease, is warranted because the biological plausibility is high and the epidemiological evidence robust. Given the prevalence of depression in primary care, FM and GIM physicians will be the largest group to apply depression, psychotropic medication, and risk of coronary heart disease: a population-based cohort study. J Int J Cardiol 2013; 168: 4711–6.

Additional research is needed to incorporate primary data collection to merge lifestyle measurements with medical record data.

Declarations
Funding: none.
Ethical approval: IRB approval was obtained prior to initiating study.
Conflict of interest: none declared.

References

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