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DEPRESSION, CARDIOVASCULAR DISEASE, DIABETES, AND 2-YEAR MORTALITY AMONG OLDER PRIMARY CARE PATIENTS

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Abstract

Objective—Depression is a major contributor to death and disability, but few follow-up studies of depression have been carried out in the primary care setting. We sought to assess whether depression in older patients is associated with increased mortality after a 2-year follow-up interval and to estimate the population attributable fraction (PAF) of depression on mortality in older primary care patients.

Method—Longitudinal cohort analysis carried out in 20 primary care practices. Participants were identified through a two-stage, age-stratified (60–74; 75+) depression screening of randomly sampled patients; enrollment included patients who screened positive and a random sample of screened negative patients. In all, 1226 persons were assessed at baseline. Vital status at 2 years was the outcome of interest.

Results—Of 1226 persons in the sample, 598 were classified as depressed. After 2 years, 64 persons had died. Persons with depression at baseline were more likely to die at the end of the 2-year follow-up interval than were persons without depression (relative odds 1.81, 95% confidence interval [1.07, 3.05]; Wald $\chi^2 = 4.96$, df = 1, $p = 0.03$), even after accounting for potentially influential covariates such as whether the participant reported a history of myocardial infarction (MI) or diabetes. We estimated the PAF due to depression on mortality to be 13%. By comparison, the PAF on mortality due to baseline report of MI was 11%; diabetes 9%; and any cardiovascular disease 18%.

Conclusions—Among older primary care patients over the course of a 2-year follow-up interval, depression contributed as much to mortality as did MI or diabetes.

Keywords

aged; depressive disorder; mortality; prospective studies; risk factors

INTRODUCTION

Many prospective studies [1–16], though not all [17–22], have found that depression increases the risk of death for older persons. Primary care occupies a strategic position in the evaluation, treatment, and prevention of the mental disturbances of late life [23–27]. In the United States, primary care has only recently drawn attention as a venue worthy of study [28]. Few follow-up studies of depression in late life, with mortality as an endpoint, have been based in primary health care [22]. In reviewing prognosis of depression among older persons, Cole and coworkers [29] cited four studies based on primary care samples. However, the cited studies provided no estimates for mortality associated with depression [30,31] or did not include a comparison group [32,33]. Similarly, in the description of her own follow-up study of 222 adults with depression in primary care [34], van Weel-Baumgarten found only one other follow-up study of depression based in primary care [35], and neither study included a comparison group. Michael Shepherd called primary health care the “middle ground for psychiatric epidemiology” [36], but the lack of sound follow-up studies of older primary care patients represents a gap in the knowledge needed to inform studies of the effectiveness of treatment.

Our investigation had two related goals. First, we wanted to assess the relationship between depression, identified with standard criteria at baseline in a representative sample of older adults seen in primary health care settings, and risk of mortality over the course of a 2-year follow-up interval. In addition, we wished to provide an estimate of the attributable fraction of mortality due to depression in older primary care patients. In other words, we wanted to provide an estimate of the number of deaths that might be prevented in the population if the influence of depression could be mitigated in older primary care patients. To accomplish these goals, we employed data from the multi-site, randomized trial, PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial). PROSPECT tested the impact of a primary care-based intervention on reducing major risk factors for suicide in late life [37]. PROSPECT's intervention combined treatment guidelines tailored for the elderly with care management. In this paper, we focus on the association of depression with mortality, independent of several potentially influential covariates, over the course of a 2-year follow-up interval.

METHODS

Study sample

The study was conducted in 20 primary care practices from greater New York City, Philadelphia, and Pittsburgh. Practices ranged in size (solo to medium sized), setting (rural, suburban and urban), population type (including two serving primarily African-American patients), and affiliation (16 community-based and four academic practices). Patients were recruited using a two-stage sampling design [38]. The study drew an age-stratified (60–74, 75 + years), random sample of patients with an upcoming appointment. Physicians notified sampled patients, by mail, allowing patients to decline contact. Research associates telephoned the remaining sample to confirm study eligibility: age ≥ 60 years, ability to give informed consent, Mini-mental Status Examination (MMSE) ≥ 18 [39], and ability to communicate in English. With oral consent, eligible patients were screened for depression using the Centers for Epidemiologic Studies Depression scale (CES-D) [40].

Eligibility criteria

The study invited all patients scoring CES-D > 20 [41], as well as a 5% random sample of patients with lower scores, to enroll in the research protocol. The purpose of the 5% sample was to assess for “false negative” cases of screened depression. To increase the screen's

sensitivity, patients scoring ≤ 20 and not selected randomly were recruited if they responded positively to supplemental questions about prior depressive episodes or treatment. Suicidal ideation was not included in eligibility criteria. Eligible patients met at the practice with research associates who, with signed consent, administered an in-person interview [42]. The research protocol received full review and approval from the Institutional Review Board at each of the three universities.

Assessment of the exposure variable

The exposure variable in this study was depression. In contrast to most previous community-based studies whose measures of depression were often based on symptom scales [8–10,12,14,16,19,22], we have direct clinical assessments of depression status consistent with DSM-IV [43]. PROSPECT conducted a full Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) assessment, allowing for the full range of DSM-IV diagnoses for depressive disorders, including major depression, minor depression (DSM-IV provisional criteria), brief recurrent depression, and dysthymia [44].

In order to reduce the likelihood of site-related differences in the application of diagnostic criteria for major depression, the Cornell Intervention Research Center (IRC) implemented regular teleconferences among research assistants at all IRCs to review diagnostic practices and to conduct formal reliability assessment. Interviewer training included: (1) observation and discussion of interviews employing the SCID; (2) concurrent with watching tapes, observation of several interviews of patients illustrating a range of severity of depression; (3) practice of at least two role plays of the interviews based on examples provided in the SCID training materials; and (4) interview of at least two patients who are not participating in PROSPECT with in-person supervision. We asked that research assistants audiotape 30 randomly selected interviews (10 from each PROSPECT site) and review the tapes with the other research assistants from each site, independently rating tapes to ensure consistency in diagnosis. Ongoing monitoring indicated excellent reliability within and across sites for SCID (intraclass correlation (ICC) range 0.78 to 1.0).

Covariates under study

Sociodemographic characteristics were assessed with standard questions regarding age, gender, level of educational attainment, self-identified ethnicity, and marital status. Smoking status was based on report of current smoking (within 6 months of interview). Participants were asked about lifetime occurrence of myocardial infarction (MI), heart failure, angina, angioplasty or coronary artery bypass surgery, atrial fibrillation, and diabetes. Persons were considered to have any cardiovascular disease (CVD) if they gave a positive response to any of the following: myocardial infarction, heart failure, angina, angioplasty, coronary artery bypass surgery, or atrial fibrillation.

Assessment of vital status

Vital status in this investigation was based on follow-up of participants during research interviews. We noted when the research assistant attempted to reach the participant for an interview and was told the respondent had died, or when the contact person (provided by the participant at the start of the study) told the research assistant that the respondent had died. All deaths were confirmed against a search of the National Death Index. Overall sensitivity of the NDI for ascertainment of vital status was 98% in the Nurses Health Study [45] and has generally been well over 90% in most studies (see Sathiakumar et al. [46] for a review).

Analysis strategy

Our analysis proceeded in two phases. In the first phase, we investigated the impact of depression status on mortality and the additional influence of MI and CVD. Baseline demographic characteristics and disease rates were compared for those participants, identified as depressed by the SCID, to those without depression. A discrete-time survival analysis was conducted using standard logistic regression models [47]. As suggested by Willett and Singer, we have arranged the data in a “person-period” format where each person has a record for each data collection period. Each record contains: (1) time indicators for 4, 8, 12, 18, and 24 months; (2) predictor variables; and, (3) an indicator of vital status (coded ‘1’ if the death occurred during that time interval and ‘0’ otherwise). Specifically, the model for the dependence of the risk of death on depression status and MI is as follows:

$$\text{logit}(h_j) = \alpha_0 T_4 + \alpha_1 T_8 + \alpha_2 T_{12} + \alpha_3 T_{18} + \alpha_4 T_{24} + \beta_1 \text{DEPRESSED} + \beta_2 \text{MI},$$

where h_j represents the hazard probability in time period j . In this equation β_1 and β_2 represent the influence of baseline depression and MI, respectively, on the logit hazard function. Relative odds and 95% confidence intervals are reported for the measure of association of depression and MI on mortality. We introduced a term in the model, representing the interaction between baseline depression and MI status, to test whether the effect of depression on mortality differed between persons who reported MI at baseline and persons who did not. We carried out an additional set of analyses, replacing MI by any CVD.

In the second phase of the analysis, we wanted to estimate the population attributable fraction of death due to depression. The population attributable fraction (PAF) estimates the proportional amount that risk of death would be reduced if depression were eliminated from the population [48]. The PAF, a function of the proportion of the exposed population (p_e) and the adjusted relative odds of mortality associated with depression (RO), is calculated by the following equation [48,49]:

$$\text{PAF} = \frac{p_e(\text{RO} - 1)}{1 + (p_e(\text{RO} - 1))}.$$

This formula assumes there is no confounding of the exposure-disease association. By design, the PROSPECT study over sampled for depressed participants, so the sample estimate of exposure is an overestimate of the exposed population proportion (p_e). We used sampling weights to estimate the prevalence of depression in the population of older persons who attended the practices, during the period of study, for use in calculation of the PAF. In order to compare the PAF of depression on mortality after 2-year follow-up to the PAF associated with other conditions, we have also calculated the corresponding PAF associated with baseline report of MI, diabetes, and any CVD. A random effect for clustering by primary care practice was included in the full model, but the within-practice correlation was virtually zero and did not affect the results.

RESULTS

Sample characteristics

Table 1 describes the baseline characteristics, subsequently used as covariates in multivariate models, of participants who met and who did not meet criteria for depression in PROSPECT.

Relative odds of depression and 2-year mortality

The relative odds (RO) from models assessing the association between the diagnosis of depression at baseline and death in the 2-year follow-up interval are shown in Table 2. Specifically, depressed older primary care patients were 1.78 times as likely to die after a 2-year follow-up interval (95% confidence interval (CI) [1.06, 2.99]; Wald $\chi^2 = 4.79$, df = 1, $p = 0.03$) than were persons who did not meet criteria for depression at baseline. After adjusting for the presence of MI and diabetes at baseline, persons with depression were almost twice as likely to die after the 2-year follow-up interval (relative odds = 1.81, 95% CI [1.07, 3.05]; Wald $\chi^2 = 4.96$, df = 1, $p = 0.03$). There was no interaction of depression with MI at baseline on mortality risk. Results were similar when we examined the relationship between any CVD and mortality. Specifically, after adjustment for any CVD and diabetes, persons with depression were 1.75 times as likely to die after the 2-year follow-up interval (95% CI [1.04, 2.96]; Wald $\chi^2 = 4.42$, df = 1, $p = 0.04$).

Population attributable fraction due to depression and medical conditions

We estimated that the weighted proportion of the population exposed to depression to be 0.18. The estimate of 0.18 for the proportion exposed yields a PAF of 0.127, or 13%, when combined with the relative odds estimate associated with depression in Table 2. Corresponding figures for population exposure and PAF for baseline report of myocardial infarction were 0.12 and 11%; for diabetes, 0.20 and 9%; and for any heart disease, 0.14 and 18%.

DISCUSSION

In our study, the influence of depression on risk of death after a 2-year follow-up interval was independent of the presence of CVD and diabetes at baseline, with no effect modification by MI of the association between depression and mortality risk. We estimated that the attributable population fraction of death due to depression was 13%. The attributable risk of 13% means that if the influence of depression could be removed from the population from which the sample was drawn, we could expect 13% fewer deaths after a 2-year follow-up interval. The estimated PAF of 13% for depression was comparable to the PAF for both CVD and diabetes.

Before discussing the implications of our findings, we want to lay out the hazards of trying to establish a link between depression and mortality among older primary care patients. Some issues are common to all longitudinal research, while others are specific concerns that arise when one measures psychological variables, such as depression, that cannot be observed directly. Here we have the methodological limitations of similar studies relating to misclassification of exposure (e.g., depression), important covariates (e.g., medical conditions), and outcome (e.g., assuming a participant is alive at follow-up when they have died). Accuracy of depression diagnosis is particularly difficult in older persons. Depression and other forms of psychopathology may be underestimated in the elderly because many older adults minimize reports of sadness, anhedonia, and other psychological symptoms of depression secondary to physical health conditions [50–55]. Similarly, cognitive impairment in some older adults leads to under-reporting of depression [53]. The prevalence of psychopathology can be inflated by misattributing symptoms of medical illness, medication side effects, or treatment sequelae to depression. An advantage of the PROSPECT study is the use of sensitive instruments by carefully trained research staff to measure depression diagnoses and severity. Use of semi-structured clinical interviews, the SCID, allowed for thorough clinical evaluation. Interviewers were expected to respond to visual cues (tearfulness, affect, appearance, demeanor), to challenge inconsistencies (patients who report no activities, yet deny anhedonia; patients who are tearful but deny sadness), and to request clarification (is sleep disturbance because the patient wakes frequently to use the bathroom, or because rumination disturbs the ability to fall back to sleep after using the bathroom?). This contrasts sharply with

other studies based on survey instruments, retrospective recall, or non-standardized clinical assessments.

In this study, we have had to rely on patient self-reports of cardiovascular disease and diabetes. Even examination of patient charts is expensive and would still be prone to error because of incomplete recording of diagnoses and medications, especially if the patient receives care in more than one health system. Our point estimate of the association between cardiovascular disease and mortality were similar whether focusing specifically on self-reported MI or when we included all cardiovascular conditions in models. Diabetes may be underreported, and the extent to which persons with depression also have diabetes may that was not captured by our assessment process may have affected our study results.

Even with confidence in our measures of covariates and exposure, we may be misled by misspecification of the model relating depression and death. This may occur when important variables have not been included in our model (see Bollen for a detailed discussion of model misspecification and the consequences of omitting variables [56]). We may also be misled if we adjust for characteristics which are in the causal pathway (i.e., mediators are treated as confounders) because we can spuriously reach a conclusion that depression was not associated with mortality. We have tried to take care in adjusting our estimates of association for potentially influential characteristics that may relate to the outcome. We also have the problem of left censoring, in that we exclude persons for whom the event of interest, death, has taken place before the beginning of our observation period [57]. For example, if depression exerted its strongest effect on mortality in early life, possibly through its indirect effect on risk factors for CVD, we may underestimate the level of risk. Although one study found depression expressed decades earlier was associated with death in late life [58], many studies have found a significant association among older adults based on depression assessments over fairly short time horizons [1,4,7,8,59,60]. Even if misspecification occurs due to left censoring, from a public health perspective there was value in evaluating whether depression was associated with risk of death and in assessing the attributable risk of death due to depression.

Despite limitations, our results deserve attention because there are few follow-up studies of older adults from primary health care settings and none have estimated the attributable risk of depression on mortality, as we have done here. Callahan et al. reported mortality risk related to depression among older primary care patients, but that study was not based on clinical assessments (high depressive symptom score was not statistically associated with mortality [22]).

There have been several follow-up analyses of the Epidemiologic Catchment Area (ECA) community samples that were interviewed in New Haven, Connecticut (15 months of follow-up [1] and after 9 years of follow-up [61]), the Durham-Piedmont region of North Carolina (1 year of follow-up [17]), and Baltimore, Maryland (15 years of follow-up [62]). Despite consistency in measurement strategy, there were inconsistent results in the estimates of association for depression and mortality from the ECA. In New Haven, among adults aged 55 years and older, affective disorder present within 6 months of baseline interview was associated with an adjusted risk estimate of 2.97 (95% CI [1.12, 7.92]; [1]). Focusing on adults aged 40 years and older who were interviewed in the New Haven ECA, after a 9-year follow-up interval, the risk of death among persons with major depression within 6 months of the baseline interview was 2.01 (adjusted for potentially influential characteristics assessed at baseline ($p < 0.001$); [61]). In contrast, a 1-year follow-up study of persons aged 60 years and older from the Duke University site of the ECA did not show a strong association between depression and mortality (adjusted relative risk 1.15, 95% CI [0.73, 1.81]; [14]). Compared to the studies from the New Haven ECA, the Duke ECA study did not make use of the depression diagnoses from the Diagnostic Interview Schedule (DIS) and was based on a smaller sample and shorter follow-

up interval. Based on a 15-year follow-up of the Baltimore ECA, a lifetime diagnosis of a depressive disorder, derived from DIS interviews at baseline, was associated with an adjusted risk estimate of 1.2 (95% CI [0.6, 2.4]; [62]). This 1981 estimate was based on study of the entire sample, aged 18 years and older, and was not focused on the older adults in the sample. In another study based on the Baltimore ECA, follow-up focused on adults aged 50 years and older at baseline. Persons who reported depressive symptoms that included hopelessness and thoughts of death (but not dysphoria) were at increased risk of death compared to persons without significant depression (adjusted relative risk 1.84, 95% CI [1.09, 3.09]; [6]). In contrast to the follow-up studies from the ECA program, our study employed a sample from primary care settings, enriched with persons with depression, who were assessed clinically at baseline.

Even among older adults, depression contributes significantly to mortality risk, especially in the context of medical conditions such as cardiovascular disease and diabetes. We estimated that about 1 in 10 deaths would be prevented if the influence of depression could be eliminated from the population from which our sample was drawn. The estimate of PAF for deaths due to depression was comparable to the PAF associated with medical conditions reported at baseline. Depression may lead to despair and suicide. Among older adults who are depressed, suicide accounts for only a small proportion of deaths. Most depressed older adults die from other causes such as CVD. We know from other work that, for many aspects of care, primary care clinicians prefer mental health care to be integrated with primary health care for older patients with psychiatric disturbances [63]. If we are to deal effectively with depression as a public health problem, we need to address practice re-design to better integrate treatment for chronic medical and mental health conditions, to tailor services to the patient, and to take into account patient expectations and values.

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Table 1

Characteristics of the study sample according to depression diagnosis at baseline assessment. Data from the PROSPECT study (2001–2003). CVD, cardiovascular disease; MI, myocardial infarction; s.d., standard deviation. Percents in parentheses are based on the total number in the corresponding column.

	Total sample (n=1226)	Depression diagnosis (n=599)	No depression diagnosis (n=627)	Statistic _[df] (p)
Age, mean in years (s.d.)	71 (7.8)	70 (7.9)	72 (7.7)	$t_{(1224)}=3.52$ (0.0004)
Education, mean in years (s.d.)	13 (5.1)	13 (4.2)	13 (5.8)	$t_{(1218)}=2.31$ (0.0212)
Women (%)	857 (70)	429 (72)	428 (68)	$\chi^2_{(1)}=1.54$ (0.2150)
Ethnic minority (%)	373 (30)	179 (30)	194 (31)	$\chi^2_{(1)}=0.16$ (0.6879)
Married (%)	471 (39)	220 (37)	251 (40)	$\chi^2_{(1)}=1.36$ (0.2438)
Smoker (%)	90 (7)	50 (9)	40 (6)	$\chi^2_{(1)}=1.91$ (0.1665)
CVD (%)	213 (18)	118 (20)	95 (15)	$\chi^2_{(1)}=5.24$ (0.0221)
MI (%)	183 (15)	100 (17)	83 (13)	$\chi^2_{(1)}=3.49$ (0.0618)
Diabetes (%)	260 (22)	123 (21)	137 (22)	$\chi^2_{(1)}=0.19$ (0.6627)
Deaths (%)	64 (5)	38 (6)	26 (4)	$\chi^2_{(1)}=2.99$ (0.0838)

Table 2

Relative odds of death after a 2-year follow-up interval according to personal characteristics, depression, diabetes, and myocardial infarction assessed at baseline. Multivariate models based on discrete-time survival analysis. PROSPECT data (2001–2003). LL, log likelihood; MI, myocardial infarction; RO, relative odds.

	Model A		Model B		Model C	
	RO	95% CI	RO	95% CI	RO	95% CI
Age (years)	1.05	(1.02, 1.09)	1.05	(1.02, 1.09)	1.06	(1.02, 1.09)
Women	0.39	(0.23, 0.66)	0.42	(0.25, 0.73)	0.43	(0.25, 0.74)
Ethnic minority	0.86	(0.48, 1.56)	0.88	(0.48, 1.59)	0.85	(0.47, 1.55)
Married	0.81	(0.47, 1.42)	0.82	(0.47, 1.44)	0.83	(0.47, 1.45)
Education (years)	0.96	(0.89, 1.03)	0.97	(0.90, 1.04)	0.97	(0.91, 1.04)
Smoker	0.35	(0.11, 1.17)	0.35	(0.11, 1.17)	0.34	(0.10, 1.14)
Depression	1.78	(1.06, 2.99)	1.76	(1.05, 2.96)	1.81	(1.07, 3.05)
MI			2.18	(1.25, 3.80)	2.08	(1.19, 3.65)
Diabetes					1.49	(0.85, 2.61)
-2LL(χ^2)	639.307		631.889		629.896	