A Systematic Review of the Mortality of Depression

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Objective: The literature on the mortality of depression was assessed with respect to five issues: 1) strength of evidence for increased mortality, 2) controlling for mediating factors, 3) the contribution of suicide, 4) variation across sample types, and 5) possible mechanisms. **Method:** All relevant English language databases from 1966 to 1996 were searched for reviews and studies that included 1) a formal assessment of depressive symptoms or disorders, 2) death rates or risks, and 3) an appropriate comparison group. **Results:** There were 57 studies found; 29 (51%) were positive, 13 (23%) negative, and 15 (26%) mixed. Twenty-one studies (37%) ranked among the better studies on the strength of evidence scale used in this study, but there are too few comparable, well-controlled studies to provide a sound estimate of the mortality risk associated with depression. Only six studies controlled for more than one of the four major mediating factors. Suicide accounted for less than 20% of the deaths in psychiatric samples, and less than 1% in medical and community samples. Depression seems to increase the risk of death by cardiovascular disease, especially in men, but depression does not seem to increase the risk of death by cancer. Variability in methods prevents a more rigorous meta-analysis of risk. **Conclusion:** The studies linking depression to early death are poorly controlled, but they suggest that depression substantially increases the risk of death, especially death by unnatural causes and cardiovascular disease. Future well-controlled studies of high risk groups may guide efforts to develop treatments that reduce the mortality risk of depression. **Key words:** depression, affective disorders, death, mortality.

MI = myocardial infarction.

INTRODUCTION

During the last three decades more than 50 published studies of the mortality of depression have contributed to the common belief that depression increases the risk of early death. Recently, several well-designed, controlled studies have suggested that some depressed populations have as much as a four-fold increase in risk of death, compared with nondepressed control groups (1–5). However, other well-designed studies have found either no increased risk of death (6–8) or mixed results (9–11). A few narrative reviews of these studies of the mortality of depression have been published (12–17), but none has systematically reviewed all mortality studies to assess the strength of the evidence for a relationship between depression and early death.

This review of the English language literature on the mortality of depression during the last 30 years (1966–1996) addressed several questions. First, how strong is the evidence for increased mortality in people with a history of depression? Second, how well do these studies control for the most important mediating factors? Third, how much does suicide account for the increased mortality rates? Fourth, how does the evidence vary across sample types (community, psychiatric, and medical samples)? And fifth, what do these studies suggest about possible mechanisms by which depression might increase the risk of death?

Previous studies of the mortality of depression have varied widely in sample selection, measures of depression, choices of comparison groups, analytic methods, and the factors controlled for in analyzing the relationship between depression and mortality. This methodological variability poses problems for the synthesis of the evidence. For example, how shall we compare the mortality ratio in a 40-year follow-up of psychiatric inpatients in Iowa assessed by psychiatric examination in the 1930s (9) to an odds ratio in an 18-month follow-up of post-MI patients in Montreal assessed by the Diagnostic Interview Schedule in 1991? The interpretation of results across this group of mortality studies has also been confused by selective attention to positive results and relative neglect of the negative results when multiple mortality outcome measures are reported in "mixed" studies. In addition, most reviews and studies have referred only to a small portion of the existing mortality studies. A systematic review of the methods and results of all the available mortality studies may clarify what we know and what we do not know about the strength of the relationship between depression and early death. If we can identify who among the depressed are at greatest risk for early death, we may establish a basis for intervention studies.

Four factors repeatedly have shown strong associa-

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tions with both depression and increased mortality: chronic physical illness (8, 18), smoking (19), alcohol abuse (20), and in psychiatric populations, suicide and related "accidents" (16). Although other factors are also associated with depression and death (21), we believe these four are the most important mediating factors of the relationship between depression and early death.

METHOD

In addition to informal collections, consulting experts, and cross referencing, we searched the MEDLINE, PsychInfo, and Health databases from 1966 through 1996, English language citations only, crossing "depression" and "affective disorders" with "mortality" and "death" as subject headings. Drawing from more than 200 citations collected through these databases and informal searches, we selected studies that 1) assessed the contribution of depression to the risk of death, 2) assessed depressive symptoms or depressive disorders by clinical diagnosis, structured interview, or a standard symptom inventory, and 3) compared death rates in a depressed sample with death rates in a comparison group. We excluded studies of bereavement and studies of single symptoms of depression (such as hopelessness or depressed mood). When we found several reports on a single study sample, we selected the one report that best represented the mortality data. We included all reports of bipolar disorder that specifically assessed the mortality of bipolar depression.

To assess the strength of the evidence, we rated four components of each study's methods: sample size, measure of depression, choice of comparison group, and factors controlled for, according to a priori values set by us for variations in methods (see Appendix). For sample size: $N > 500$ rated 3, $N = 100$ to 500 rated 2, and $N < 100$ rated 1. For measures of depression: structured diagnostic interview rated 3, psychiatric examination or post hoc application of diagnostic criteria rated 2, and self-report measure rated 1. For comparison groups: matched control groups rated 3, cohorts (depressed vs. nondepressed, survivors vs. nonsurvivors, etc.) rated 2, and general population rated 1. For factors controlled for: age, sex, and two of the four major mediating factors (physical illness, smoking, alcohol, and suicide) rated 3; age, sex and one of the four major mediating factors rated 2; and age and sex only, or other minor mediating factors rated 1. We defined the "better studies" as those that earned a total strength of evidence rating of 9 or greater (possible range 4–12).

A positive study was defined as one that reported all measurements of mortality risk to be significantly increased at the $p < .05$ level, at least. A negative study reported no significant increase in any measurement of mortality risk. A mixed study reported both positive and negative measurements of mortality risk (such as positive in men but negative in women or positive at 40 years follow-up but negative at 10 years).

RESULTS

Strength of Evidence

There were 57 studies (Table 1) that met our inclusion criteria. Among these studies, we identified 29 (51%) positive studies, 13 (23%) negative studies, and 15 (26%) mixed studies.

Twenty-one studies (37%) earned a strength of evidence rating of 9 or greater and were classified as the "better studies" (Table 2). Of these 21 studies, 10 (48%) were positive, 6 (29%) were negative, and 5 (23%) were mixed. This distribution among the better studies is similar to the distribution among the whole sample of 57 studies.

Relative mortality was assessed by mortality ratios (31 studies ranging from 0.6 to 7.3), relative risks (15 studies ranging from .82 to 2.1), and odds ratios (8 studies ranging from 1.1 to 7.8). On the basis of sample type and study methods, we identified three groups of comparable studies within which to summarize estimates of risk. Group 1 included studies of psychiatric samples assessed by psychiatric examination, compared with population mortality rates, controlling for age and sex, with outcomes measured by mortality ratios. In this group we found 18 studies (10, 11, 25, 28, 30, 32, 33, 35–38, 40, 43, 45, 47, 52, 55, 58) with a weighted average mortality ratio of 2.7 (range = 0.6–7.3). Group 2 included studies of community samples assessed by self-report measures, comparing depressed to nondepressed subjects, controlling for at least one major mediating factor, with outcomes measured by relative risk. In this group we found five studies (2, 7, 57, 60, 64) with a weighted average relative risk of 1.2 (range = .82–1.6). Group 3, the most methodologically rigorous group, included studies of medical or community samples assessed by structured interview, comparing depressed to nondepressed subjects, controlling for physical illness, with outcomes measured by relative risk. In this group we found four studies (1, 3, 4, 66), all among the better studies, with a weighted average relative risk of 1.7 (range = 1.6–1.8). Because of differences in assumptions underlying the computation of odds ratios, we did not calculate summary statistics for the studies that reported only odds ratios.

Mediating Factors

Table 3 lists most of the factors controlled for in the 57 studies and the number of studies that controlled for each factor. In addition to age and sex, severity of physical illness and level of functioning were the most commonly controlled variables. Remarkably, during the first two decades reviewed (1966–1986) only 1 of the 19 studies controlled for any of the four major mediating factors (severity of physical illness, smoking, alcohol, suicide) in addition to age and sex. However, during the last decade (1987–1996) 30 of 38 studies have controlled for at least one major mediating factor. But only seven studies have controlled for two (2, 3, 5, 31, 60, 62, 63) and one study (66) has controlled for all four major mediating factors. Only nine

TABLE 1. The Studies

Study Author and Year	Sample[a]	Depression Measure	Comparison Groups	Controlled for	Percent of Sample Deceased	Excess Mortality Among Depressed[b]	Suicide as Percent of Deaths Among Depressed	Comments [Strength of Evidence Rating]
Perris and d'Elia, 1966 (22)	797 affective disease inpts,[c] Sweden 1950–63, 14-yr. follow-up (psych.)	Psychiatric examination	Population	Age, sex	11 for unipolar; 23 for bipolar		7 for males, 15 for females	(±) study [7]; increased mortality for bipolar but not unipolar patients
Bratfos and Huag, 1968 (23)	215 bipolar inpts, Norway, 1952–61, 6-yr. follow-up (psych.)	Psychiatric examination	General population	Age, sex	16	16% in bipolar vs. 6% in general population	12	(+) study [6]
Babigian and Odoroff, 1969 (24)	39,475 psychiatric pts, Monroe City, 1960–6, 6-yr. follow-up (psych.)	Psychiatric examination	Population	Age, sex	10	2.1 for males; 1.9 for females (relative risk; significance not reported)		(+) study [7]; risks also increased for other psychiatric disorders
Kerr et al., 1969 (25)	135 affective disorder inpts, England, 1963–65, 4-yr. follow-up (psych.)	Psychiatric examination	Population	Age, sex, duration of follow-up	11	3.1* for males only; 2.4 for females	13	(±) study [6]; 1 of 2 mortality measures significantly elevated
Rorsman, 1974 (26)	3623 psychiatric pts, Lund, Sweden, 1962, 6-yr. follow-up (psych.)	Psychiatric examination	Surviving psychiatric patients	Age, sex	7	.92 for males; .64 for females		(−) study [8]; MR for total psychiatric sample was 1.8* for males, 1.4* for females
Avery and Winokur, 1976 (27)	519 depressed inpts, Iowa, 1959–69, 3-yr. follow-up (psych.)	Feighner criteria for primary affective disorder	Adequate treatment vs. inadequate treatment	Age, sex	6.2	9.9% in inadequate rx vs. 4% in adequate rx	1.5	(+) study [8]; no comparison with nondepressed group
Kay and Petterson, 1977 (28)	69 bipolar inpts, Sweden 1900–10, 50-yr. follow-up (psych.)	Psychiatric examination	Population	Age, sex	93	1.7* for males; 1.9* for females	4.7	(+) study [5]
Tsuang and Woolson, 1978 (9)	685 depression, mania, schizophrenia inpts, Iowa, 40-yr. follow-up (psych.)	Psychiatric examination	Surgical disorders only; schizophrenia; mania	Age, sex, duration of follow-up	53	.9 (approx.) at 40-yr. follow-up	8	(±) study [8]; 2 of 8 mortality measures increased; MR = 2* at 10-yr. follow-up; suicide and accidents account for increased risk
Persson, 1981 (29)	292 Swedish citizens, 70-yr. old, 1971–2, 5-yr. follow-up (comm.)	Psychiatric examination	Survivors vs. nonsurvivors	Age, sex	14	No association		(−) study [7]; mortality related only to "organic" disorders in men
Coryell, 1981 (30)	152 depression, somatization disorder inpts, 1925–50, 42-yr. follow-up (psych.)	Psychiatric examination; Feighner unipolar depression	Females with somatization disorder; population	Age, sex, duration of follow-up	53	1.1 at 40-yr follow-up	14.3	(±) study [7]; 1 of 5 mortality ratios significantly increased; MR = 3.2* at 10-yr. follow-up
Shekelle et al., 1981 (31)	2020 employed men, 40–55 yr. old, WEHS, 17-yr. follow-up (comm.)	MMPI, depressive symptoms	Nondepressed sample	Age, **smoking**, **alcohol**,[d] family history of cancer, occupation	19	2.2*, for cancer (odds ratio); 1.3 for noncancer	<1	(±) study [9]; 1 of 2 mortality measures significantly increased
Eastwood et al., 1982 (32)	585 psychiatric inpts, Toronto, 1969, 9.5-yr. follow-up (psych)	Psychiatric examination	General population	Age, sex	11	1.4*; 7.5* for unnatural deaths; 1.0 for natural deaths	31 for "unnatural deaths"	(+) study [6]

Coryell et al., 1982 (10)	225 depression, panic inpts, 1925–55, 35-yr. follow-up (psych.)	Psychiatric examination; Feighner unipolar depression	Panic disorder; population	Age, sex, duration of follow-up	29	2.2* for males; 2.4* for females (at 30-yr. follow-up)	16.2	(±) study [7]; 5 of 10 mortality ratios significantly increased
Haugland et al., 1983 (33)	1033 psychiatric inpts, 1975–76, 3.5-yr. follow-up (psych.)	Psychiatric examination, DSM II affective disorders	Schizophrenia; alcoholism; population	Age, sex	8	3.2*		(+) study [8]; alcoholism and schizophrenia also had increased mortality ratios
Norton and Whalley, 1984 (34)	791 lithium treated pts, Scotland, 1967–76, 10-yr. follow-up (psych.)	Psychiatric examination, Feighner affective disorders	33 age and sex matched controls	Age, sex	44	2.8*	24	(+) study [9]; combines unipolar and bipolar data
Rabins et al., 1985 (35)	62 depressed inpts, >60 yrs. old, 1-yr follow-up	Psychiatric examination, DSM III major depression	Population	Age, sex, age of onset, number of episodes, delusions	13	2.6 (significance not reported)	3.2	(+) study [5]
Black et al., 1985 (11)	4869 psychiatric inpts, Iowa, 1972–81, 10-yr. follow-up (psych.)	Psychiatric examination, ICD 9 affective disorders	Population; other psychiatric disorders	Age, sex	6	1.1 for males; 1.4* for females	37 ("unnatural causes")	(±) study [8]; 7 of 16 mortality ratios significantly increased; major effect in first 2 yr. after discharge
Martin et al., 1985 (36)	500 psychiatric outpts, St Louis 1967–69, 12-yr. follow-up (psych.)	Modified Feighner affective disorders	Population	Age, sex, race	9	0.8 for primary; 3.1* for secondary depression	0 in primary unipolar; 5.7 in secondary unipolar	(±) study [6]; 1 of 3 mortality ratios significantly increased
Weeke and Vaeth, 1986 (37)	2168 bipolar and unipolar inpts, Denmark, 1970–72, 7-yr. follow-up (psych.)	Psychiatric examination, unipolar major depression	Population; bipolar group	Age, sex	14	2.2* for males; 1.5* for females	25	(+) study [8]
Weeke et al., 1987 (38)	3995 bipolar inpts, 1950–76, Denmark, 3-yr. follow-up (psych.)	Psychiatric examination, bipolar depression	General population	Age, sex, tricyclic treatment	13	2* for TCA era group; 2.5* for pre-TCA era group	37	(+) study [7]
Murphy et al., 1987 (39)	1003 Stirling County citizens, 1952–70, 16-yr. follow-up (comm.)	Structured lay interview, affective disorders	Nondepressed sample	Age, sex, **physical disorder**	24	1.5 (significance not reported)	<1	(±) study [10]; MR for depressed males 2.1, for female 1.2
Black et al., 1987 (40)	1593 affective disease inpts, Iowa 1970–81, 13-yr. follow-up (psych.)	DSM III, major depression and bipolar dis.	Population; bipolar group	Age, sex, **physical disorder**	10	7.3* for unnatural death; 1.2 for natural death	31	(±) study [10]; 5 of 8 mortality ratios increased; no increased ratio for natural deaths
Berglund and Nisson, 1987 (41)	1206 depressed inpts, Sweden 1956–69, 27-yr. follow-up (psych.)	Essen-Moller diagnostic schedule	Population	Age, sex, **suicide**	40	1.3* for males; 1.2* for females	22	(+) study [7]
Kaplan and Reynolds, 1988 (42)	6848 Alameda County citizens, 1965–82, 17-yr. follow-up (comm.)	HPL questionnaire, depressive symptoms	Nondepressed sample	Age, sex	18	1.6* for noncancer; 1.1 for cancer (rel hazard)	<1.4	(±) study [7]; 2 of 4 mortality risks increased; no increased risk for cancer mortality
Murphy E, et al., 1988 (43)	321 depressed pts + controls, >65 yr. old, London, 1979–80, 4-yr. follow-up (psych.)	Present State Exam, Feighner primary depression	Age- and sex-matched community control group; population	Age, sex, **physical illness**	34	1.7* for females; 1.9 for males	2.4	(+) study [10]; excess mortality persists when controlling for physical illness

TABLE 1. (*Continued*)

Study Author and Year	Sample[a]	Depression Measure	Comparison Groups	Controlled for	Percent of Sample Deceased	Excess Mortality Among Depressed[b]	Suicide as Percent of Deaths Among Depressed	Comments [Strength of Evidence Rating]
Mayou et al., 1988 (44)	457 medical inpts, Oxford, UK, 1-yr. follow-up (med.)	Present State Exam	Age- and sex-matched control group of medical inpatients	Age, sex, **physical illness**, treatment	14	2		(−) study [10]; no statistically significant increase in death rat among depressed
Lee and Murray, 1988 (45)	89 depressed inpts, London, 1965–6, 17-yr. follow-up (psych.)	RDC major depression	Population	Age, sex	16	1.9*	28	(+) study [5]
Koenig et al., 1989 (46)	82 depressed medical inpts, 1-yr. follow-up (med.)	DSM III R, major depression	Nondepressed matched control group	Age, **severity of illness**, and level of functioning, diagnosis	37	6 dead in depressed vs. 0 in controls*, in-hospital only	0	(±) study [8]; 1 of 2 mortality rates increased; no increase for patients discharged from hospital
Zonderman et al., 1989 (7)	6410 US citizens, NHANES, 1971–75, 15-yr. follow-up (comm.)	CES-D, General Well-being Schedule	Nondepressed	Age, sex, marital status, **smoking**, family history, hypertension, cholesterol	2	1.2 (adjusted relative risk)		(−) study [9]; assessed effect of depression on cancer deaths only
Zilber et al., 1989 (47)	1574 affective disorder inpts, Israel, 1978, 5-yr. follow-up (psych.)	Psychiatric examination	General population	Age, sex, ethnic origin	19	1.5*	2	(+) study [6]
Fredman et al., 1989 (6)	1606 elderly citizens, ECA Study, 1982–83, 2-yr. follow-up (comm.)	DSM III major depression or dysthymia	Population >65	Age, sex, race, education, social status, level of functioning, **severity of illness**	5.9	1.1 (MR); 0.9 (relative risk)		(−) study [9]
Bruce and Leaf, 1989 (48)	3007 US citizens >55 yr. old, ECA Study, 1.3-yr. follow-up (comm.)	DIS, depressive disorders	Other psychiatric disorders, and no psychiatric disorders	Age, sex, **physical disorder**	4.5	1.8* lifetime disorder, 3.0** recent (odds ratios)	0	(+) study [10]; affective disorders and schizophrenia had similar risks of death
Silverstone, 1990 (49)	211 medical inpts, England, .1-yr. follow-up	MADRS, adjustment disorder with depressed mood	Nondepressed medical inpatients	Age, sex, **severity of illness**	10	14.2% depressed vs. 1.3% nondepressed	0	(+) study [7]
Roberts et al., 1990 (50)	8023 Alameda County citizens, 1965, 18-yr. follow-up (comm.)	HPL Index of psychological dysfunction	Nondepressed	Age, sex, education, **physical illness**, disability, perceived health	36	1.1 (odds ratio)	<1	(−) study [8]; significant risk vanishes with controlling for confounders
Ahern et al., 1990 (51)	502 post-MI patients with arrhythmias (med.)	BDI	Survivors vs. nonsurvivors	Age, sex, **cardiac functioning**, personality, social support, mood		1.4* (relative risk)		(+) study [7]
Vestergaard and Aagaard, 1991 (52)	133 affective disease pts on lithium, 1981–83, Denmark, 5-yr. follow-up (psych.)	Feighner depression or mania	General population	Age, sex, **comorbidity**, marital status, life events	17	4.4*	23	(+) study [7]
Rovner et al., 1991 (1)	454 nursing home patients, Baltimore, 1987–88, 1-yr. follow-up (med.)	Present State Exam, depressive disorder and symptoms	Nondepressed nursing home patients	Age, sex, treatment, level of functioning, hospitalization, **severity of illness**	31	1.6* for depressive disorder only; (relative risk)		(±) study [9]; 1 of 2 mortality risks increased; no excess mortality for depressive symptoms

Jorm et al., 1991 (53)	274 Australian citizens >70 yr. old, 1882–3, 5-yr. follow-up (comm.)	DSM III major depression, depressive symptoms	Nondepressed	Age, sex, physical functioning, cognitive functioning	29	1.5 (relative risk)		(−) study [8]; significant risk vanishes with controlling for physical illness
Ladwig et al., 1991 (54)	570 males, 3 wk after MI, Germany, 1983–85, .5-yr. follow-up (med.)	Ksb-S, major depression	Group with low depression scores	Age, social status, medical history, **cardiac status**	2	7.5% in depressed vs 0.9% in nondepressed group*†		(+) study [8]; risk reduced almost to insignificance with controlling for confounders
Muller-Oerlinghausen et al., 1992 (55)	827 lithium pts, 5 sites, 7-yr. follow-up (psych.)	Psychiatric examination	General population	Age, sex	11	.89	2	(−) study [7]; suggests lithium treatment decreases mortality rate
Brill et al., 1992 (56)	406 men, Dallas, 1970–86, 9-yr. follow-up (comm.)	Clinical Analysis Questionnaire	83 cases vs. 323 population controls; depressed vs. nondepressed	Age, fitness, anxiety	20	2.1 (adjusted odds ratio for low fitness group)		(−) study [8]; depression and anxiety do not change the relationship between fitness and mortality
Thomas et al., 1992 (57)	1855 Bronx citizens, >65, 1984, 3-yr. follow-up (comm.)	CES-D, depressive symptoms	Depressed vs. nondepressed	Age, sex, **severity of illness**, social support, level of functioning	9	.82 (relative risk)		(−) study [8]
Parmelee et al., 1992 (8)	898 elderly, Philadelphia, 1985–88, 1.5-yr. follow-up (comm.)	SADS, major and minor depression	Survivors vs. nonsurvivors; depressed vs. nondepressed	Age, sex, cognitive status, **health status**, functional status	16	2.5 for major; 1.3 for minor depression (odds ratio)		(−) study [10]; significant risk vanishes with controlling for functional disability and perceived health
Anda et al., 1993 (2)	2832 US adult citizens, NHEFS, 17-yr. follow-up (comm.)	General Well-Being Schedule, depressive symptoms	Ischemic heart disease vs. no ischemic heart disease	Age, sex, race, educ., marital status, **smoking**, cholesterol, blood pressure, body mass, **alcohol**, physical activity	7 (by ischemic heart disease)	1.5* for fatal ischemic heart disease (adjusted relative risk)		(+) study [9]; adjusted relative risk for fatal ischemic heart disease was also increased for hopelessness, 2.1*
Morris et al., 1993 (3)	103 stroke inpts, 2 wk. after stroke, Baltimore 1980, 10-yr. follow-up (med.)	Present State Exam, DSM III, major depression and dysthymia	Survivors vs. nonsurvivors	Age, sex, social class, type of stroke, level of functioning, **alcohol use**, **medical illness**	53	1.7* (relative risk); 3.4* (odds ratio)		(+) study [10]
Sharma and Markar, 1994 (58)	472 bipolar pts, Edinburgh, 1970–75, 17-yr. follow-up (psych.)	Psychiatric examination, DSM III bipolar disorder	General population, matched survivor group	Age, sex		3* for cardiovascular and respiratory disorders; 23.4* for suicide	1.7	(+) study [8]
Aromaa et al., 1994 (59)	5355 Finnish citizens, age 40 or over, 6.6-yr. follow-up (comm.)	Present State Exam, General Health Questionnaire	Depressed vs. nondepressed	Age, sex, education, cardiac risk factors, **physical illness**	4.4	1.8*		(+) study [11]; MR increased for cardiovascular deaths, but not for cancer deaths
Bruce et al., 1994 (4)	3560 New Haven ECA Study, citizens >40 yrs, 9-yr. follow-up (comm.)	DIS, depressive disorders	Nonpsychiatrically ill sample	Age, sex, psychiatric comorbidity, **alcohol**	34	2.0* for recent, 1.5 for past depression, (relative risk)	<1	(±) study [10]; 1 of 3 mortality risks significantly increased
Vogt et al., 1994 (60)	2573 adults, Kaiser HMO, Oregon, 1970–1, 15-yr. follow-up (comm.)	Authors' depression index	Depressed vs. nondepressed	Age, sex, **health status**, social status, **smoking**		.91 (adjusted relative hazard)		(−) study [9]; no measures of mental health, anxiety, or depression predicted mortality

TABLE 1. (*Continued*)

Study Author and Year	Sample[a]	Depression Measure	Comparison Groups	Controlled for	Percent of Sample Deceased	Excess Mortality Among Depressed[b]	Suicide as Percent of Deaths Among Depressed	Comments [Strength of Evidence Rating]
Frasure-Smith et al., 1995 (5)	222 MI hospital pts, 1 wk. after MI, Montreal 1991–2, 1.5-yr. follow-up (med.)	DIS, BDI; major depression, and depressive symptoms	Survivors vs. nonsurvivors	Age, sex, **severity of cardiac dysfunction**, previous MI, social status, social support, **smoking**	9	3.6* major depression; 7.8* for depressive symptoms; (adjusted odds ratio)	0	(+) study [10]; major depression affects MR in first 6 mo.; depressive symptoms affect MR throughout 18 mo.
Simonsick et al., 1995 (61)	10,294 US citizens, EPESE study, over 64-yr. old, hypertension, 1982–3, 6-yr. follow-up (comm.)	CES-D	Group with low depression scores	Age, sex, **disability**, diabetes, angina, digitalis use, history of MI and stroke		>2* for Iowa women only		(±) study [8]; 3 (all female) of 6 mortality rates significantly increased at 6-yr. follow-up
Denollet et al., 1995 (62)	105 men with recent MI, Antwerp, 1986–89, 3.8-yr. follow-up (med.)	Depression scale of Millon Behavioral Health Inventory	Survivors vs. nonsurvivors	Age, **cardiac status**, **smoking**, personality type	14	2*	0	(+) study [9]; distressed personality type predicts cardiac mortality
Denollet et al., 1996 (63)	303 adults in cardiac rehab., Antwerp, 1985–88, 7.9-yr. follow-up (med.)	Depression scale of Millon Behavioral Health Inventory	Survivors vs. nonsurvivors	Age, **cardiac status**, **smoking**, personality type	13	1.6*	0	(+) study [9]; distressed personality type predicts cardiac mortality
Barefoot and Schroll, 1996 (64)	730 Danish citizens, born 1914, 27-yr. follow-up (comm.)	MMPI	Nondepressed sample	Age, sex, blood pressure, triglycerides, **smoking**, activity	39	1.6* (relative risk)		(+) study [9]; mortality risk was proportional to severity of depressive symptoms
Barefoot et al., 1996 (65)	1250 angiography pts, 1974–80, 19-yr. follow-up (med.)	Zung Self-report Depression Scale	Nondepressed	Age, sex, **severity of heart disease**, treatment, income	48	1.8* (adjusted relative risk)		(+) study [8]
Vaillant et al., 1996 (66, and unpublished data)	240 Harvard men, 1940–42, 50-yr. follow-up (comm.)	DSM III affective spectrum disorder	Personality disorder or alcoholism; or no psychiatric illness (rest of sample)	Age, **smoking**, **alcohol**, **severity of illness**, **suicide**	26	1.8 (relative risk)	20	(−) study [9]; controlling for smoking and alcohol makes effect of depression no longer significant
Roach et al., 1998 (67)	3529 seriously ill hospitalized adults, SUPPORT, 1989–94, .5-yr. follow-up (med.)	Depression scale of Profile of Mood States	Survivors vs. nonsurvivors	Age, sex, **severity of illness**, physical functioning	67	1.1 (odds ratio)		(+) study [8]; depressed mood was more potent predictor of death at 6 mo. than age or comorbid illness

[a] Sample drawn from general population = comm. (community); sample drawn from inpatient or outpatient psychiatric services = psych. (psychiatric); sample drawn from inpatient or outpatient medical services = med. (medical).
[b] Ratio of observed mortality vs. expected mortality for a comparison group, unless otherwise stated.
[c] BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies-Depression scale; DIS = Diagnostic Interview Schedule; DSM = Diagnostic and Statistical Manual; ECA = Epidemiologic Catchment Area study; EPESE = Established Populations for Epidemiological Studies of the Elderly; HPL = Human Population Laboratory; ICD = International Classification of Diseases; inpts = inpatients; KSb-S = Kleinische Selbstburteilungsskalen; MADRS = Montgomery Asberg Depression Rating Scale; MI = myocardial infarction; MMPI = Minnesota Multiphasic Personality Inventory; MR = mortality ratio; NHANES = National Health and Nutrition Examination Survey; NHEFS = National Health Examination Follow-up Study; outpts = outpatients; pts = patients; RDC = Research Diagnostic Criteria; rx = treatment; SADS = Schedule for Affective Disorders and Schizophrenia; SUPPORT = Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments; TCA = tricyclic antidepressant; UK = United Kingdom; WEHS = Western Electric Health Study.
[d] Bold type indicates a major mediating factor.
* $p = <.05$.

TABLE 2. Results by Sample Type for the Better Studies

Sample Type[a]	Positive	Negative	Mixed	Totals (%)[b]
Community	4	5	3	12 (63)
Psychiatric	2	0	1	3 (12)
Medical	4	1	1	6 (50)
Totals	10	6	5	21 (37)

[a] Community = sample drawn from general population; psychiatric = sample drawn from inpatient or outpatient psychiatric services; medical = sample drawn from inpatient or outpatient medical services.
[b] Percent of all studies of this sample type.

TABLE 3. Most Common Factors Controlled for by the Studies

Factor	No. of Studies (%)
Age (yr)	57 (100)
Sex	52 (91)
Severity of physical illness[a]	25 (44)
Level of functioning[b]	10 (18)
Smoking	9 (16)
Social status[c]	8 (14)
Alcohol	5 (9)
Social support[d]	5 (9)
Treatment[e]	4 (7)
Duration of follow-up	4 (7)
Suicide	3 (5)
Race	3 (5)

[a] Includes health status, cardiac status, medical history, medical comorbidity, diagnosis, type of stroke, severity of heart disease, history of MI or stroke, blood pressure, stroke, angina, cholesterol, triglycerides, diabetes. Bold denotes a major mediating factor.
[b] Includes cognitive functioning, physical functioning, disability, fitness, activity.
[c] Includes education, occupation, income.
[d] Includes marital status.
[e] Includes digitalis use, hospitalization.
[f] Includes age of onset, delusions, number of episodes, anxiety.

of all of the studies controlled for smoking and five controlled for alcohol. Of the three studies that controlled for both smoking and alcohol, one was positive, one negative, and one mixed.

Suicide

There were 35 studies that reported rates of suicide as a percentage of deaths among the depressed, ranging from 0% to 64%, with a mean of 10.8%. Only 1 of the 31 community or medical studies reported a suicide rate above 1% (66) for the depressed group. Among the 23 studies of psychiatric samples that reported suicide rates as a percentage of deaths among the depressed, suicide accounted for a mean of 16% (0%–64%) of the deaths. Although 31 studies reported suicide rates, only 3 studies included suicide among the factors controlled for in regression analyses. Among the better studies, nine reported suicide rates (0%–31%, mean = 7.3%). The rates among the three better studies of psychiatric samples were 2.4%, 24%, and 31% (mean = 19.1%).

Sample Type

We found 19 studies of community samples, 26 studies of psychiatric samples, and 12 studies of medical samples. Table 2 shows the number of positive, negative, and mixed studies by sample type for the better studies. Most of the community studies (12/19, 63%) ranked among the better studies, but few (3/26, 12%) of the psychiatric studies ranked among the better studies.

Causes of Death

There were 42 studies that reported data on causes of death, including 25 reporting data on cardiovascular deaths and 21 on cancer deaths. Of the 25 studies reporting on cardiovascular causes of death, 15 reported a significant increase, 5 reported no significant increase, and 5 reported both positive and negative findings. Four of the five mixed studies reported increased rates of cardiovascular death in men but not in women; the fifth study reported an increase in women but not men.

Of the 20 studies reporting data on cancer deaths, 4 reported a significant increase, 11 reported no significant increase, and 3 reported both positive and negative findings. (Two studies did not report significances.) In the mixed studies, there was no pattern of sex distribution. The data on causes of death are general and usually do not specify disease types, nor do they identify specific pathological mechanisms by which death occurred. These studies also fail to distinguish between deaths due to poor self-care and natural deaths.

DISCUSSION

How strong is the evidence that depression increases mortality? Not strong enough to answer the question definitively. Although it is tempting to interpret the predominance of positive studies (51%) as support for an increased risk, the meaning of this finding is limited by 1) the well-known publication bias in favor of positive studies, 2) our finding that the evidence is poorly controlled, even in the better studies, and 3) limitations to the comparability of studies.

Almost half of the studies report mixed or negative results and the large number of negative results suggests that in a substantial proportion of the popula-

tions studied, depression may confer no increased risk of death. Three studies (27, 38, 55) attribute normal or reduced death rates to the effect of antidepressant treatments, which suggests that in the psychiatric studies treatment may contribute to the variability of outcomes. Only four studies controlled for the effect of treatment (1, 38, 44, 65). The mixed studies fail to explain their conflicting results (eg, males vs. females, symptoms vs disorders, short- vs long-term follow-up, "natural" vs. "unnatural" deaths) and, with one exception mentioned below, we have been unable to find a pattern of results across mixed studies.

Although our systematic ratings of strength of evidence according to the studies' methods identified 21 "better studies," we feel these studies as a group are still not yet good enough, primarily because most fail to control for more than one of the major mediating factors. We cannot emphasize strongly enough the importance of controlling for ill health, smoking cessation failure, alcohol abuse, and suicide before postulating a causal link between depression and mortality. Over the last decade, mortality studies of depression have grown more sophisticated in their use of rigorous measures of depression and in their attention to mediating factors during design and analysis. However, we still have only eight studies (2, 3, 5, 31, 60, 62, 63, 66) that have controlled for more than one of the four major mediating factors.

In the positive studies, what accounts for the increased risk of death? In all but one of the 26 community and medical sample studies, suicide accounts for less than 1% of reported mortality. In the psychiatric studies, suicide accounts for 16% to 19% of the mortality, on the average, a figure that is consistent with the often quoted rate of 15% completed suicides among patients with severe depressive disorders. Thus suicide explains a small but important fraction of the total mortality associated with depression.

As Glassman (19) points out, smoking is associated with depression and is a potent contributor to increased mortality risk. Depressed medical and psychiatric populations seem at greater risk for premature death than community populations and the data on causes of death suggest that depression may increase death by cardiovascular disease, both through a direct effect and through poor self-care. The four of five studies (10, 26, 37, 39, 61) reporting significantly increased risks of cardiovascular death for men but not women suggest that depressed men may run a higher risk of cardiovascular death than depressed women. Alternatively, this pattern may be an artifact of greater smoking, alcohol abuse, and completed suicide in men.

These mortality studies rarely offer speculations on the mechanisms by which depression may increase the risk of early death. The major mediating factors suggest several indirect ways by which depression could cause death, such as poor self-care in the context of a physical illness, increased smoking and alcohol consumption, and increased suicidal behaviors. Everson et al. (21) have presented evidence that hopelessness may increase cardiovascular mortality independent of clinical depression. Other more direct effects, such as decreased heart rate variability and increased platelet aggregation (5, 68, 69), may only affect those with coronary artery disease. Mechanisms by which depression affects mortality after a medical event, such as a MI or a stroke, are likely to be different than the mechanisms by which depression affects death in a representative community sample.

The data on sample types show that, although almost half of the studies examined psychiatric samples, only three ranked among the better studies. What we know about the mortality of depression in psychiatric patients is based mostly on a large number of poorly controlled studies.

This review has three limitations. First, although this is the most comprehensive review of studies published in English that we know of, it does not include non-English language studies. Second, this review, like all reviews, suffers from the tendency of journals to publish positive studies, to the neglect of negative studies. Furthermore, the traditional definition of a positive study has relied too much on the p value and too little on the effect size (70), clouding our view of the true effect of depression on early mortality. And, third, because a standard system for rating study methods does not yet exist, we have created a simple system (see Appendix) for rating the strength of evidence linking mortality to depression. A different rating system would result in the selection of a different set of "better studies."

The most rigorous analysis this data allows is the systematic "nonstatistical meta-analysis" approach to literature reviews that we have applied (71). This approach, as described by Brand, improves on the common narrative review by systematically compiling the relevant data on all studies and computing summary data where possible, but it stops short of rigorous meta-analysis when the samples, analytic methods, or the exposure variables are not comparable. Our three groups of comparable studies illustrate the limits of generalizability in this data set. Group 1, the largest group ($N = 18$) and the weakest methodologically, suggests that the mortality ratio for psychiatric samples in poorly controlled studies is about 2.7, a substantial effect that is similar to the weighted average found in the review of mortality in bipolar disorder by

Goodwin and Jamison(14). However, the better controlled community studies of Group 2 ($N = 5$), limited in value by their self-report measures of depression and the small number of studies, suggest a marginally increased relative risk of 1.2. And in Group 3 ($N = 4$), the most methodologically sound, the relative risks approximate 1.7, a substantial effect that is difficult to generalize because of the small number of studies. [The number of studies would be somewhat larger ($N = 7$) if we could include in this group studies that reported only odds ratios, but it is not statistically sound to average odds ratios.]

The 1995 study by Frasure-Smith et al. (5) plus the four in Group 3 (1, 3, 4, 66) represent the state of the art in mortality studies of depression. They prospectively assessed depression by structured interview and symptom severity measures in a well-defined sample controlling for at least physical illness and one other major mediating factor using either a case-control or cohort design. Presentation of outcomes in terms of relative risks, rather than odds ratios, allows more readily for comparisons across studies.

CONCLUSIONS

These findings lead us to several conclusions and recommendations for future research on the mortality of depression:

1. The existing body of studies, so rich with mixed findings and so lean in the numbers of well-controlled comparable studies, suggests a substantial effect of depression on mortality in some populations, but to estimate the true size and the source of this effect (whether it is a direct result of the pathophysiology of depression or the indirect result of poor self-care) will require more rigorous study.
2. We propose that a model study of the mortality of depression should include a prospective longitudinal case-control or cohort design assessing a large sample (> 500) of community, medical, or psychiatric populations using structured diagnostic interviews as well as standard symptom severity scales for defining depression, while controlling through logistic regression or a comparable method for at least the four major mediating factors: physical illness, smoking, alcohol, and, in psychiatric samples, suicide and accidents.
3. Because the link between depression and cardiovascular death is the strongest known association, research on mechanisms should now focus on the effects of depression on the cardiovascular system and whether treatment can reduce the increased risk of death.

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Appendix

Strength of Evidence Rating System[a]

Category	Rating	Criteria
Sample	3	$N > 500$
	2	$N = 100$–500
	1	$N < 100$
Measure of depression	3	Structured diagnostic interview
	2	Psychiatric examination; post hoc application of diagnostic criteria
	1	Self-report measure
Comparison group	3	Matched control group
	2	Cohort (depressed vs. nondepressed, survivors vs. nonsurvivors, etc.)
	1	Population
Factors controlled for	3	Age, sex, and 2 of 4 major confounders (physical illness, smoking, alcohol, suicide)
	2	Age, sex, and 1 of 4 major confounders
	1	Age, sex only, or other minor confounders

[a] Scoring totals: 9–12 = better study; 4–8 = meets inclusion/exclusion criteria.