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Is it hypnotics that kill, or is it psychiatric illness?

Re: **Hypnotics' association with mortality or cancer: a matched cohort study**. **Kripke**, et al. ***2*:*1 e000850***

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Kripke et al. (1) raised an important concern in reporting high mortality in people using zolpidem and similar hypnotics. Already, several patients in our community health center have asked whether zolpidem is going to kill them. One primary care provider here now refuses to prescribe zolpidem citing this report and counseling his patients about the dangers of these medications. These concerns and decisions led us to read the paper, along with related studies, to settle the issue for ourselves.

Although the claim that, "in 2010, hypnotics may have been associated with 320 000 to 507 000 excess deaths in the USA alone," is alarming and most certainly deserves further study, as it stands, this report is not a secure foundation for clinical decision-making about the use of hypnotics because it does not control for psychiatric and substance use disorders.

Contributions of depression, anxiety and substance use disorders to mortality in primary care. In the last paragraph of Discussion, the authors disclose that, "we were unable to control for depression, anxiety and other emotional factors because of Pennsylvania laws protecting the confidentiality of those diagnoses," and that, "our findings might reflect some confounding by those conditions." While alcohol and tobacco use disorders were addressed, there is no mention of contributions to mortality from opioid, cocaine, cannabis or other psychoactive use conditions in this report. Although psychiatric and substance use conditions are not likely to be the only uncontrolled confounds in this study, it is prudent to consider the effects of these conditions, since they are very common in primary care. Others who have reported elevated mortality hazard in people given hypnotics have spelled this out quite clearly. Mallon et al. (2) reported a risk ratio of 3.285 for hypnotic use, but went on to state, "the increased mortality found among hypnotic users in this study may in fact be related to underlying diseases and their management rather than the hypnotic medication used."

In our view, failure to control for psychiatric conditions, including most substance abuse and dependence conditions, should constrain practitioners from employing Kripke et al.'s findings for clinical decision support and policy development in primary care settings.

Depression, insomnia and mortality related to other medical conditions. In the remainder of our remarks, we focus on depression since interaction of depression with other medical conditions has been extensively studied. Here are the major findings related to the issue addressed by Kripke et al.(1):

1. **Depression is common in people attending primary care settings.** Using conservative diagnostic criteria equivalent to the DSM-IV definition of major depressive episode, several recent studies have shown current rates of serious depression in primary care practices that exceed those seen in general population surveys. Ansseau et al. (3) reported that 6.3 percent of people visiting general practitioners in Belgium met DSM-IV criteria for depression. Ostler et al. (4) reported a rate of 7.2% for probable depression using the HADS among 18 414 people attending 55 representative practices in Hampshire. Wittchen et al. (5) identified major depressive episodes in 6.0 percent of 20 000 people attending 558 primary care practitioners in Germany. While screening 18 456 primary care attendees in typical primary care waiting rooms in six international cities, Simon et al. (6) found that 6.5 percent of subjects met the DSM-IV criteria for current depressive episode.
2. **Depression is present in a majority of people currently reporting insomnia in primary care.** Insomnia is generally considered a risk factor for development of depression (7). In a survey just

published, depression was present in 50 percent of primary care patients who reported difficulty sleeping. (8) Young people reporting insomnia are 4 times more likely than those without insomnia to report depression at 3.5 year follow-up. (9)

3. **Insomnia is present in an overwhelming majority of people with depression.** In cross-national studies of the epidemiology of depression, insomnia was the most commonly reported symptom of depression. (10) In a representative sample of people in metropolitan Toronto interviewed by telephone, insomnia was present in 75.5 percent of people who met DSM-IV criteria for any current mood disorder. (11)

We hypothesize that many patients seen in primary care who complain about insomnia are suffering from depression which goes unrecognized and untreated since they do not mention other depressive symptoms and their practitioners do not ask about these other symptoms. We also hypothesize that unrecognized and/or untreated depression contributes more to the increased mortality of people taking hypnotics than do the hypnotics themselves. In the NIMH ECA longitudinal surveys of prevalence of psychiatric disorders, (12) the odds ratio for depression was 35.0 in people with current insomnia, but only 1.6 in people who reported insomnia at baseline but no longer had insomnia at follow-up. (13) Comparing associations between chronic insomnia and depression in two surveys of the same population 11 years apart, Neckelmann et al. (14) found that only those with insomnia at follow-up had a significant increase in depression (OR=1.8).

If our hypotheses are correct, we should be able find associations between depression and mortality in studies of outcomes in all the major illness categories studied by Kripke et al.(1)

We reviewed literature of the last 10 years relating depression to mortality in the 12 general illness categories reported by Kripke et al.(1), and for cancer and all-cause mortality. To do this, we searched MedLine for the MESH terms “depression” and “mortality” in addition to MESH terms representing each major illness category. For example, we searched for “depression” and “mortality” and “asthma” and so forth for each major illness category. We found that for 11 of these illness classes, as well as for cancer and all-cause mortality, morbidity and/or mortality hazard ratios were elevated in subjects with markers of depression. Some of the recent papers reporting on depression and mortality for specific illness classes are given in Table 1.(18-49)

Comparative effects on health outcomes. The importance of controlling for depression is highlighted by a recent study (15) in which mortality associated with depression (HR = 1.52) was comparable to that for smoking (HR = 1.59)

Anhedonia may be more deleterious than sadness. Two recent studies shed particular light on what features of depression might heighten mortality. In a study of one-year outcomes following acute coronary syndromes, anhedonia, but not sadness, correlated with mortality. (16) In another recent study, the increased risk of death (HR = 1.31) in people with depression and coronary heart disease disappeared after controlling for self-reported physical activity. (17) Taken together, these findings suggest that by compromising healthy life style choices, self-care and help seeking behaviors, anhedonia and related phenomena (apathy, anergia, abulia) contribute to mortality of depression in people with other major illnesses. This is especially important because anhedonia is more likely to be overlooked, in primary care settings than overt sadness, thus contributing to the failure to recognise and treat depression.

How anhedonia might impact on outcomes in medically ill patients. These studies call to mind the many people we treat for depression in our community health center, who very often report things like this:

- “When I am depressed, I don’t do anything. I don’t want to do anything.”

- “I think of things I should do, but I don’t have any get up and go.”

- “I don’t care about anything when I am like this.”

- “I cringe when the phone rings, and I often don’t call back when friends leave a message.”

- “When neighbors walk by, I go inside.”

- “I didn’t get the mail for weeks. Then the mailman came to the door because there was no more room in the box.”

Typically and to varying degrees, seriously depressed people are also lax in taking regular exercise, in filling prescriptions and taking medications, even for major medical conditions. Cleaning up around the house, bathing and showering, brushing teeth, and preparing nutritionally adequate meals similarly suffer from neglect.

To sum up, although Kripke et al.(1) studied people given hypnotics for insomnia, findings in large population epidemiological studies require us to suspect that insomnia was a symptom of depression, or another psychiatric condition, or a substance use condition which, due to local confidentiality laws, was not discoverable by the research team. So also, we must suspect that, for most illness categories, the mortality of hypnotic use was a proxy for the mortality of psychiatric and substance use conditions in people with major medical illness, acting primarily through diminished self-care and help-seeking behaviors and eventuating in increased mortality due to their co-morbid medical conditions . The real killer is not the over-use of hypnotics, but the under-treatment of depression and other psychiatric conditions and substance abuse conditions in primary care.

Conflicts of interest: None reported

References

(1) Kripke 2012: Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. BMJ Open 2012;2:e000850. Print 2012.

(2) Mallon L, Broman JE, Hetta J. Is usage of hypnotics associated with mortality? Sleep Med 2009;10:279-86

(3) Ansseau M, Fischler B, Dierick M, et al. Prevalence and impact of generalized anxiety disorder and major depression in primary care in Belgium and Luxemburg: the GADIS study. Eur Psychiatry 2005;20:229-35.

(4) Ostler K, Thompson C, Kinmonth AL. Influence of socio-economic deprivation on the prevalence and outcome of depression in primary care: the Hampshire Depression Project. Br J Psychiatry 2001;178:12-7.

(5) Wittchen HU, Kessler RC, Beesdo K. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry 2002;63 Suppl 8:24-34.

(6) Simon GE, Fleck M, Lucas R, et al. Prevalence and predictors of depression treatment in an international primary care study. Am J Psychiatry 2004;161:1626-34.

(7) Lustberg L, Reynolds CF. Depression and insomnia: questions of cause and effect. Sleep Med Rev 2000;4:253-262.

(8) Arroll B, Fernando A 3rd, Falloon K, et al. Prevalence of causes of insomnia in primary care: a cross-sectional study. Br J Gen Pract 2012;62:99-103.

(9) Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411-8.

(10) Weissman MM, Bland RC, Canino GJ et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA 1996;276:293-9.

(11) Ohayon MM, Shapiro CM, Kennedy SH. Differentiating DSM-IV anxiety and depressive disorders in the general population: comorbidity and treatment consequences. Can J Psychiatry 2000;45:166-72.

(12) Regier DA, Myers JK, Kramer M, et al. The NIMH Epidemiologic Catchment Area program. Historical context, major objectives, and study population characteristics. Arch Gen Psychiatry 1984;41:934-41.

(13) Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA 1989;262:1479-84.

(14) Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. SLEEP 2007 30:873-80.

(15) Mykletun A, Bjerkeset O, Overland S, et al. Levels of anxiety and depression as predictors of mortality: the HUNT study. Br J Psychiatry 2009;195:118-25.

(16) Davidson KW, Burg MM, Kronish IM, et al. Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome. Arch Gen Psychiatry 2010;67:480-8.

(17) Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. JAMA 2008;300:2379-88.

Table 1: Depression's Impact on Outcomes in Major Physical Illness

1. Asthma and Depression.

(18) Jiang CQ, Loerbroks A, Lam KB, et al. Mental Health and Asthma in China: the Guangzhou Biobank Cohort Study. Int J Behav Med 2012; Feb 2. [Epub ahead of print, not in March 2012 issue]

Compared to those without depression, the prevalence of asthma was higher in those with moderate or severe depression levels (PR = 2.63, 95% CI = 1.58-4.40 and PR = 4.43, 95% CI = 1.62-12.09, p for trend ≤0.0001). The prevalence of asthma increased by 46% with every 1 standard deviation increase of the GDS-C score (PR = 1.46, 95% CI = 1.24-1.7

(19) Trzcińska H, Przybylski G, Kozłowski B, et al. Analysis of the relation between level of asthma control and depression and anxiety. Med Sci Monit 2012;18(3):CR198-202.

Individuals with depression were characterized by a significantly lower degree of asthma control compared to depression-free individuals (p<0.001). The degree of asthma control decreased significantly with increasing severity of depression (R=-0.367; p<0.001).

2. Cerebrovascular Disease and Depression.

(20) Allan LM, Rowan EN, Firbank MJ, et al. Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. Brain 2011;134:3716-27.

Univariate and multivariate regression analyses showed that the most robust predictors of dementia (HR = 1.13) and death (HR = 1.06) in non-demented stroke survivors >75 years of age included (1) low (1.5 standard deviations below age-matched control group) baseline Cambridge Cognitive Examination executive function and memory scores, (2) Geriatric Depression Scale score and (3) three or more cardiovascular risk factors. The mechanism by which depression leads to poor survival, and its interaction with dementia, urgently require further investigation.

(21) Pan A, Sun Q, Okereke OI, et al. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA 2011;306:1241-9.

Depression is associated with a significantly increased risk of stroke (HR = 1.25) and fatal stroke (HR = 1.55) in 317 540 cases included in this metanalysis of 28 prospective studies.

(22) Ried LD, Jia H, Feng H, et al. Selective serotonin reuptake inhibitor treatment and depression are associated with poststroke mortality. Ann Pharmacother. 2011;45:888-97.

Depression diagnosis was associated with greater risk of stroke mortality (HR 1.87; 95% CI 1.24 to 2.82).

3. Coronary Heart Disease and Depression.

(23) Connerney I, Sloan RP, Shapiro PA, et al. Depression is associated with increased mortality 10 years after coronary artery bypass surgery. Psychosom Med 2010;72:874-81.

Depression, assessed by structured interview and BDI was significantly associated with elevated cardiac mortality (HR = 1.8) ten years after CABG surgery

(24) Ahto M, Isoaho R, Puolijoki H, et al. Stronger symptoms of depression predict high coronary heart disease mortality in older men and women. Int J Geriatr Psychiatry 2007;22:757-63.

The Kaplan-Meier survival curves showed stronger symptoms of depression to be related to high risks of mortality from CHD or MI among men and women without CHD at baseline and followed for 12 years. According to the Cox model for men significant predictors for higher risk of CHD or MI mortality were stronger symptoms of depression, higher age and a large number of medications in use.

(25) Prescott E, Holst C, Grønbaek M, et al. Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study. Int J Epidemiol 2003;32:990-7.

The 17 items on the vital exhaustion questionnaire were frequently endorsed with prevalence ranging from 6 to 47 per cent, higher in women. All but 4 of the 17 items were significantly associated with IHD with significant relative risks (RR) ranging between 1.36 (95% CI: 1.08, 1.72) and 2.10 (95% CI: 1.63, 2.71). Associations with all-cause mortality were also observed, but were weaker. RR of both IHD and all-cause mortality increased with increasing item sum score and were similar in men and women. For IHD, RR reached a maximum of 2.57 (95% CI: 1.65, 4.00) for subjects endorsing >9 items. The similar RR for all-cause mortality was 2.50 (95% CI: 2.09, 2.99)

4. Chronic Kidney Disease and Depression.

(26) Halen NV, Cukor D, Constantiner M, et al. Depression and mortality in end-stage renal disease. Curr Psychiatry Rep 2012;14:36-44.

Depression is the most prevalent co-morbid psychiatric condition, estimated at about 25% of end-stage renal disease samples.

(27) Kellerman QD, Christensen AJ, Baldwin AS, et al. Association between depressive symptoms and mortality risk in chronic kidney disease. Health Psychol 2010;29:594-600.

Mortality HR = 1.24 for people exceeding mean depression ratings by one SD who had mild CKD at baseline and were followed for mean 81 months or until death. After controlling for relevant mortality risk factors (i.e., age, gender, presence of diabetes and cardiovascular disease, and potassium level), results of Cox regression analyses indicated that higher levels of non-somatic depression symptoms were predictive of an increased mortality risk, $\chi^2(1, N = 359) = 8.02$, $p = .005$. Patients with non-somatic depression scores 1 SD above the mean had an estimated mortality rate 21.4% higher than average scorers in this sample.

(28) Hedayati SS, Minhajuddin AT, Afshar M, et al. Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. JAMA 2010;303:1946-53.

The presence of an MDE was associated with an increased risk of poor outcomes in CKD patients who were not receiving dialysis, independent of comorbidities and kidney disease severity. The mean (SD) time to the composite event was 206.5 (19.8) days (95% CI, 167.7-245.3 days) for those with an MDE compared with 273.3 (8.5) days (95% CI, 256.6-290.0 days) for those without an MDE (P = .003). The adjusted hazard ratio (HR) for the composite event for patients with an MDE was 1.86 (95% CI, 1.23-2.84). An MDE at baseline independently predicted progression to dialysis (HR, 3.51; 95% CI, 1.77-6.97) and hospitalization (HR, 1.90; 95% CI, 1.23-2.95).

(29) Hedayati SS, Jiang W, O'Connor CM, et al. The association between depression and chronic kidney disease and mortality among patients hospitalized with congestive heart failure. Am J Kidney Dis 2004;44:207-15.

After controlling for important clinical factors, severe CKD was associated with depressive symptoms by BDI (odds ratio, 2.89; 95% confidence interval, 1.39 to 5.99). Both depression by DIS and severe CKD were significant predictors of mortality. The increased mortality risk associated with depression did not decline with decreasing kidney function.

5. Chronic Obstructive Pulmonary Disease and Depression.

(30) De Voogd JN, Wempe JB, Koëter GH, et al. Depressive symptoms as predictors of mortality in patients with COPD. Chest 2009;135:619-25

Depressive symptoms (odds ratio [OR], 1.93; 95% confidence interval [CI], 1.12 to 3.33) were associated with mortality in patients with COPD, independent of other factors including male sex (OR, 1.73; 95% CI, 1.03 to 2.92), older age (OR, 1.05; 95% CI, 1.02 to 1.08), and lower Wpeak (OR, 0.98; 95% CI, 0.97 to 0.99).

(31) Ng TP, Niti M, Tan WC, et al. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med 2007;167:60-7.

Multivariate analyses showed that depression was significantly associated with mortality (hazard ratio, 1.93; 95% confidence interval, 1.04-3.58), longer index stay (mean, 1.1 more days; P = .02) and total stay (mean, 3.0 more days; P = .047), persistent smoking at 6 months (odds ratio, 2.30; 95% confidence interval, 1.17-4.52), and 12% to 37% worse symptoms, activities, and impact subscale scores and total score on the St George Respiratory Questionnaire at the index hospitalization and 1 year later, even after controlling for chronicity and severity of COPD, comorbidities, and behavioral, psychosocial, and socioeconomic variables.

(32) Stage KB, Middelboe T, Pisinger C. Depression and chronic obstructive pulmonary disease (COPD). Impact on survival. Acta Psychiatr Scand 2005;111:320-3.

Depression in out-patients suffering from COPD appears to be an independent protector for mortality.

6. Diabetes Mellitus and Depression.

(33) Milano AF, Singer RB. Mortality in co-morbidity (II)--excess death rates derived from a follow-up study on 10,025 subjects divided into 4 groups with or without depression and diabetes mellitus. J Insur Med 2007;39:160-6.

Mortality for diabetics with depression was 1.70 fold higher than death rate expected for diabetes alone.

(34) Young BA, Von Korff M, Heckbert SR, et al. Association of major depression and mortality in Stage 5 diabetic chronic kidney disease. Gen Hosp Psychiatry 2010;32:119-24.

Major depression at baseline was associated with a 2.95-fold greater risk of mortality among stage 5 CKD diabetic patients. Given the high mortality risk, further testing of targeted depression interventions should be considered in this population.

(35) Pan A, Lucas M, Sun Q, et al. Increased mortality risk in women with depression and diabetes mellitus. Arch Gen Psychiatry 2011;68:42-50.

Compared with participants without either condition, the age-adjusted relative risks (RRs) (95% confidence interval) for all-cause mortality were 1.76 (1.64-1.89) for women with depression only, 1.71 (1.54-1.89) for individuals with diabetes only, and 3.11 (2.70-3.58) for women with both conditions. The corresponding age-adjusted RRs of CVD mortality were 1.81 (1.54-2.13), 2.67 (2.20-3.23), and 5.38 (4.19-6.91), respectively.

7. Heart Failure and Depression.

(36) Sherwood A, Blumenthal JA, Hinderliter AL, et al. Worsening depressive symptoms are associated with adverse clinical outcomes in patients with heart failure. J Am Coll Cardiol 2011;57:418-23.

Worsening symptoms of depression are associated with a poorer prognosis in HF patients, HR = 1.10 for mortablity or CV hospitalization.

(37) Kato N, Kinugawa K, Yao A, et al. Relationship of depressive symptoms with hospitalization and death in Japanese patients with heart failure. J Card Fail 2009;15:912-9.

Multivariate Cox regression analyses indicated that depressive symptoms were predictors of cardiac death or HF hospitalization (hazard ratio [HR], 3.29; P = .02), HF hospitalization (HR, 3.36; P = .04), and all-cause death (HR, 5.52; P = .01), independent of age and brain natriuretic peptide.

(38) de Denus S, Spinler SA, Jessup M, et al. History of depression as a predictor of adverse outcomes in patients hospitalized for decompensated heart failure. Pharmacotherapy 2004;24:1306-10.

The 34 patients with a history of depression had a higher likelihood of experiencing the combined end point of in-hospital death or CPR compared with the 137 patients without a history of depression (17.7% vs 6.6%, p<0.05). A history of depression (odds ratio 3.3, 95% confidence interval 1.01-10.6, p<0.05) was still predictive of in-hospital death or CPR in a multivariate analysis after adjusting for predictors of the combined end point.

8. Hypertension and Depression.

(39) Kuo PL, Pu C. The contribution of depression to mortality among elderly with self-reported hypertension: analysis using a national representative longitudinal survey. J Hypertens 2011;29:2084-90.

In the full model, the hazard ratios for mortality for the groups of not hypertensive/depressed, hypertensive/not depressed, and hypertensive/depressed were 1.12 [95% confidence interval (CI) 0.98-1.28], 1.32 (95% CI 1.19-1.46), and 1.54 (95% CI 1.29-1.83), respectively, compared with the reference group of not hypertensive/not depressed.

(40) Peters R, Pinto E, Beckett N, et al. Association of depression with subsequent mortality, cardiovascular morbidity and incident dementia in people aged 80 and over and suffering from hypertension. Data from the Hypertension in the Very Elderly Trial (HYVET). Age Ageing 2010;39:439-45.

For GDS >= 6, a strong association was found between baseline depression scores and later fatal and non-fatal cardiovascular endpoints over a mean follow-up of 2 years in a hypertensive very elderly group (all cause mortality HR = 1.8, cardiovascular mortality HR = 2.10, all stroke mortality HR = 1.8)

9. Obesity and Depression.

(41) Acosta-Pérez E, Canino G, Ramírez R, et al. Do puerto rican youth with asthma and obesity have higher odds for mental health disorders? Psychosomatics 2012;53:162-71. Epub 2012 Jan 28.

Asthma and obesity were significantly related to higher odds of depressive/anxiety disorders in youth.

10. Reflux / Peptic Disease and Depression.

No references found

11. Peripheral Vascular Disease and Depression.

(42) Cherr GS, Zimmerman PM, Wang J, et al. Patients with depression are at increased risk for secondary cardiovascular events after lower extremity revascularization. J Gen Intern Med 2008;23:629-34.

At revascularization, 35.0% patients had been diagnosed with depression. Those with depression were significantly younger and more likely to use tobacco. By life-table analysis, patients with depression had significantly increased risk for death/MACE, coronary heart disease, and contralateral PAD events, but not cerebrovascular events or death. By multivariate analysis, patients with depression were at significantly increased risk for death/MACE (hazard ratio [HR] = 2.05; p < .0001), contralateral PAD (HR = 2.20; p = .009), and coronary heart disease events (HR = 2.31; p = .005) but not cerebrovascular events or death.

(43) Cherr GS, Wang J, Zimmerman PM, et al. Depression is associated with worse patency and recurrent leg symptoms after lower extremity revascularization. J Vasc Surg 2007;45:744-50.

Depression is common among patients undergoing intervention for symptomatic PAD. After intervention, patients with depression have worse outcomes for the affected leg. By multivariate analysis, patients with depression were at significantly increased risk for recurrent symptomatic PAD (hazard ratio [HR], 1.77; 95% confidence interval [CI], 1.03 to 3.02; P = .04) and failure of revascularization (HR, 2.18; 95% CI, 1.22 to 3.88; P < .01), but not major amputation.

12. All-cause Mortality and Depression.

(44) Mykletun A, Bjerkeset O, Overland S, et al. Levels of anxiety and depression as predictors of mortality: the HUNT study. Br J Psychiatry 2009;195:118-25.

Case-level depression was associated with increased mortality (hazard ratio (HR) = 1.52, 95% CI 1.35-1.72) comparable with that of smoking (HR = 1.59, 95% CI 1.44-1.75), and which was only partly explained by somatic symptoms/conditions.

(45) Mykletun A, Bjerkeset O, Dewey M, et al. Anxiety, depression, and cause-specific mortality: the HUNT study. Psychosom Med 2007;69:323-31.

Depression is a risk factor for all major disease-related causes of death and nearly all major causes of death; the association between depression and mortality was no stronger for CVD mortality than for other causes combined.

(46) Prescott E, Holst C, Grønbaek M, et al. Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study. Int J Epidemiol 2003;32:990-7.

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(47) Fu CC, Lee YM, Chen JD. Association between depressive symptoms and twelve-year mortality among elderly in a rural community in Taiwan. J Formos Med Assoc 2003;102:234-9.

Of the 280 study participants, 94 died within the 12-year study period. Univariate analysis revealed the following significant predictors of mortality: advanced age, type of household, marital status, and CES-D score. The multivariate age-adjusted hazard ratio for depressive symptoms (CES-D score >/= 15 vs < 15) was 1.55 (95% confidence interval, 0.99 to 2.44).

(48) Ensinck KT, Schuurman AG, van den Akker M, et al. Is there an increased risk of dying after depression? Am J Epidemiol 2002;156:1043-8.

68,965 patients were followed for an average of 15 years. Among 1,362 depressed subjects 132 died, and among 67,603 non-depressed subjects 4,256 died. The adjusted hazard ratio for depressed versus non-depressed subjects was 1.39 (95% confidence interval: 1.16, 1.65).

13. Cancer and Depression.

(49) Onitilo AA, Nietert PJ, Egede LE. Effect of depression on all-cause mortality in adults with cancer and differential effects by cancer site. Gen Hosp Psychiatry 2006;28:396-402.

Compared to the reference group, the hazard ratios (HRs) for all-cause mortality were as follows: cancer but no depression HR = 1.43, depression but no cancer HR = 1.44, cancer and depression HR = 1.87.