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The Interface of Medical and Psychiatric Disorders: Focus on Cancer and Heart Disease

Presented by:

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Board of Directors: Gratitude America, ADAA, Xhale Smart, Inc.

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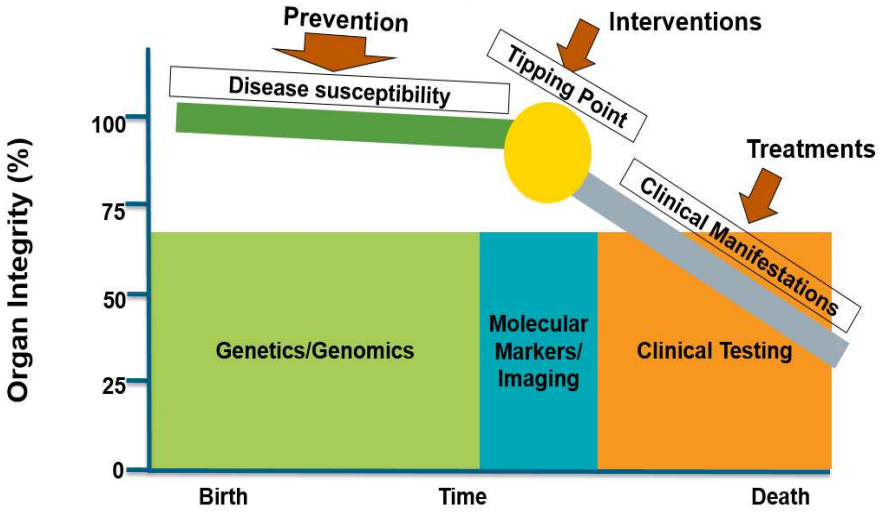
Speakers Bureau: None

21st Century Medicine



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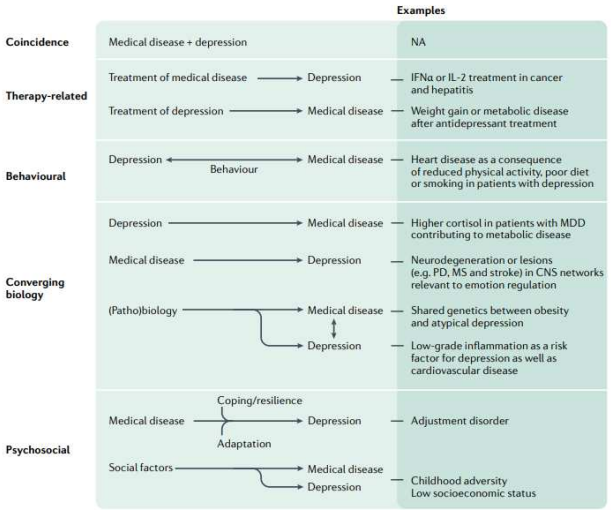

Fig. 1 | **Possible heuristic models to explain the comorbid occurrence of depression and medical diseases.** Several phenomena could link depression to a medical disease. These phenomena may include coincidence as well as several direct or indirect mechanisms such as therapy-related pathways, behavioural connections, converging biology and psychosocial factors. CNS, central nervous system; MDD, major depressive disorder; MS, multiple sclerosis; NA, not applicable; PD, Parkinson disease.

Gold, S.M., Köhler-Forsberg, O., Moss-Morris, R. *et al.* Comorbid depression in medical diseases. *Nat Rev Dis Primers* **6**, 69 (2020). https://doi.org/10.1038/s41572-020-0200-2

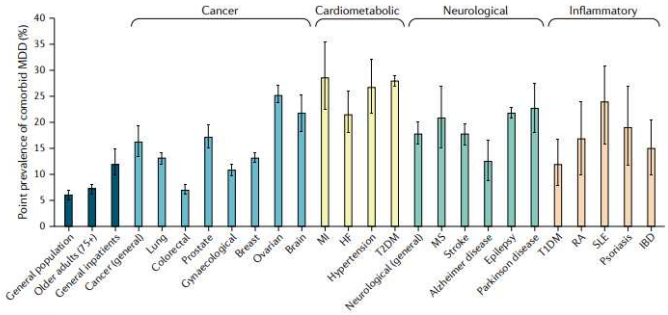

Fig. 2 | **Prevalence estimates of comorbid MDD in patients with chronic medical diseases.** The studies included in the meta-analyses showed a wide range of prevalence estimates with considerable heterogeneity reported, which could have been caused, for example, by the depression assessment instrument used, depression severity or duration of the medical disease. Hence, the values are considered approximate prevalence estimates of comorbid major depressive disorder (MDD), in which prevalence refers to the mean pooled prevalence calculated in the published meta-analyses for the specific medical diseases. Bars and error bars represent the prevalence of comorbid MDD and the 95% confidence intervals for each medical disease or disease group, respectively, as calculated in the individual meta-analyses of the general population[14,274], individuals >75 years of age[20], inpatients[22], and individuals with cancer (general)[24,25], brain cancer[28], breast cancer[275], prostate cancer[26], ovarian cancer [27], lung cancer, colorectal cancer and gynaecological cancer [276], myocardial infarction (MI)[13,14], heart failure (HF)[6], hypertension[277], type 2 diabetes mellitus (T2DM)[15], type 1 diabetes mellitus (T1DM)[30], stroke[39,40], multiple sclerosis (MS)[41], epilepsy[45], Parkinson disease[46], Alzheimer disease[47], systemic lupus erythematosus (SLE)[48], psoriasis[49], rheumatoid arthritis (RA)[50], and inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis[51]. Of note, 'cancer' includes data on several cancer types, people in palliative care or hospice settings and those who are not in palliative care, and patients with or without metastases. 'Neurological' includes data for MS, stroke, Alzheimer disease, Parkinson disease and epilepsy.

Gold, S.M., Köhler-Forsberg, O., Moss-Morris, R. *et al.* Comorbid depression in medical diseases. *Nat Rev Dis Primers* **6,** 69 (2020). https://doi.org/10.1038/s41572-020-0200-2

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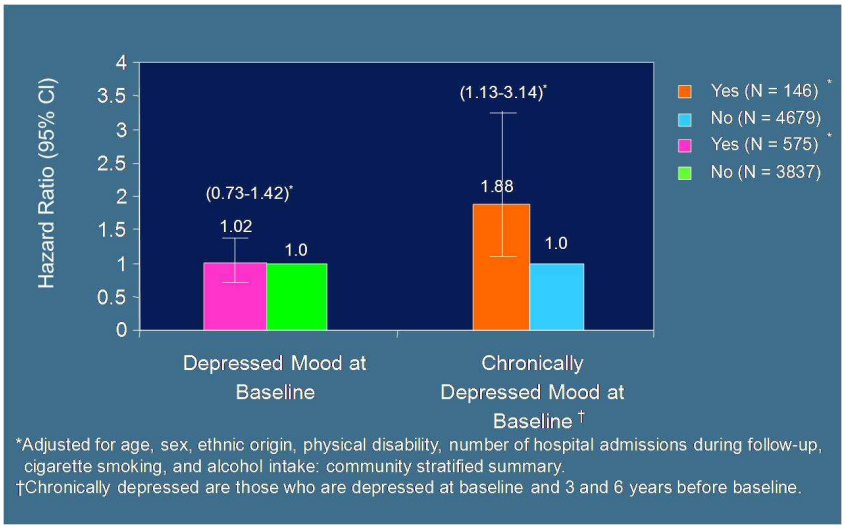
Major Depression In Cancer: Prevalence

Cancer Site	References	Prevalence (%)
Pancreas	Fras et al, 1967 Joffe et al, 1986	50
Oropharyngeal	Morton et al, 1984 Davies et al, 1986 Baile et al, 1992	40
Colon	Fras et al, 1967	13-25
Breast	Farber et al, 1984 McDaniel et al, 1993	18-25
Gynecologic	Evans et al, 1986	23
Hodgkin's and NHL	Devlon et al, 1987	17
Gastric	Joffe et al, 1986	11
Acute Leukemia, Pre-BMT	Colon et al, 1991	1-8

McDaniel JS et al. *Arch Gen Psychiatry*. 1995;52:89-99.

Is Depression a Risk Factor for Cancer?



*Adjusted for age, sex, ethnic origin, physical disability, number of hospital admissions during follow-up, cigarette smoking, and alcohol intake: community stratified summary.
†Chronically depressed are those who are depressed at baseline and 3 and 6 years before baseline.

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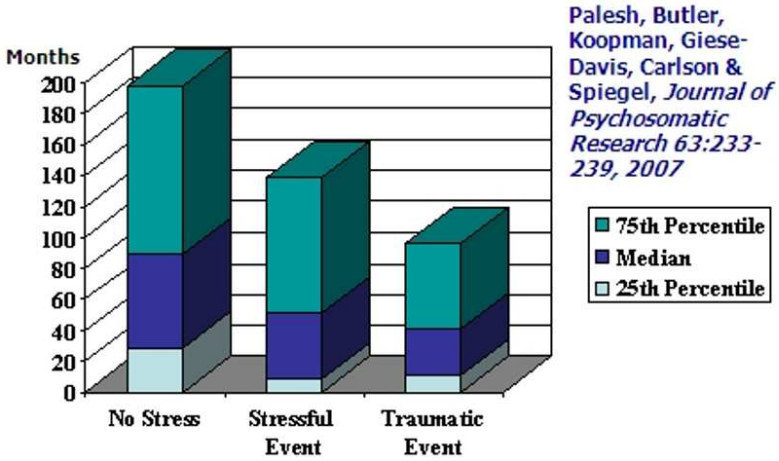
Depression and Cancer Progression

- 578 women with early stage breast cancer were enrolled in a prospective survival study.
- At 5 years, 395 women were alive and without relapse, 50 were alive with relapse, and 133 had died. There was a significantly increased risk of death from all causes by 5 years in women with a high depression score (hazard ratio 3.59, 95% CI 1.39-9.24).
- There was also significantly increased risk of relapse or death at 5 years in women with high scores on the helplessness and hopelessness measures.

Watson et al. Lancet, 354:1331-1336, 1999

Disease-Free Interval by Type of Event (Median, 25th and 75th Percentiles)



Palesh, Butler, Koopman, Giese-Davis, Carlson & Spiegel, *Journal of Psychosomatic Research 63:233-239, 2007*

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Decrease in Depression Symptoms Is Associated With Longer Survival in Patients With Metastatic Breast Cancer: A Secondary Analysis

Janine Giese-Davis, Kate Collie, Kate M.S. Rancourt, Eric Neri, Helena C. Kraemer, and David Spiegel

Median survival was 53.6 months for women with decreasing depression scores over 1 year and 25.1 months for women with increasing depression scores

J Clin Oncol 29:413-420. © 2010 by American Society of Clinical Oncology

Population and Prevention Science
Cancer Research

Psychologic Distress Is Associated with Cancer-Specific Mortality among Patients with Cervical Cancer

Donghao Lu[1,2], Bengt Andrae[1,3], Unnur Valdimarsdóttir[1,2,4], Karin Sundström[5], Katja Fall[6], Pär Sparén[1], and Fang Fang[1]

Abstract

Emerging evidence suggests a role of psychologic factors in the progression of different cancer types. However, it is unclear whether psychologic distress around the time of diagnosis of invasive cervical cancer places patients at a higher risk of cancer-specific mortality, independently of tumor characteristics and treatment modalities. We conducted a nationwide cohort study, including 4,245 patients with newly diagnosed cervical cancer during 2002–2011 in Sweden. Psychologic distress was indicated by a clinical diagnosis of depression, anxiety, or stress reaction and adjustment disorders, or the experience of a stressful life event, including death or severe illness of a family member, divorce, or between jobs, from one year before cancer diagnosis and onwards. We calculated the HRs of cancer-specific mortality among the patients exposed to psychologic distress, compared with unexposed patients, controlling for socioeconomic characteristics and other known prognostic indicators such as tumor and treatment characteristics. We found that patients exposed to psychologic distress had an increased risk of cancer-specific mortality (HR 1.33; 95% CI, 1.14–1.54). The association was primarily driven by distress experienced within one year before or after diagnosis (HR 1.30; 95% CI, 1.11–1.52), but not thereafter (HR 1.12; 95% CI, 0.84–1.49). In summary, our study shows that psychiatric disorders and stressful life events around cancer diagnosis are associated with increased cancer-specific mortality among patients with cervical cancer, independent of tumor characteristics and treatment modality.

Significance: These findings support the integration of psychologic screening and intervention in the clinical management of patients with cervical cancer, particularly around the time of cancer diagnosis.

Cancer Res 2019;79:3965–72
doi: 10.1158/0008-5472.CAN-19-0116

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Posttraumatic Stress Disorder Is Associated with Increased Risk of Ovarian Cancer: A Prospective and Retrospective Longitudinal Cohort Study

Andrea L. Roberts[1], Tianyi Huang[1,2], Karestan C. Koenen[1], Yongjoo Kim[1], Laura D. Kubzansky[1], and Shelley S. Tworoger[1,3]

ABSTRACT: Ovarian cancer is the deadliest gynecologic cancer. Chronic stress accelerates tumor growth in animal models of ovarian cancer. We therefore postulated that posttraumatic stress disorder (PTSD) may be associated with increased risk of ovarian cancer. We used data from the Nurses' Health Study II, a longitudinal cohort study with 26 years of follow-up, conducted from 1989 to 2015 with 54,710 subjects. During follow-up, 110 ovarian cancers were identified. Women with high PTSD symptoms had 2-fold greater risk of ovarian cancer versus women with no trauma exposure [age-adjusted HR ¼ 2.10; 95% confidence interval (CI), 1.12–3.95]. Adjustment for health and ovarian cancer risk factors moderately attenuated this association (HR ¼ 1.86; 95% CI, 0.98–3.51). Associations were similar or moderately stronger in fully prospective analyses (age-adjusted HR ¼ 2.38; 95% CI, 0.98–5.76, N cases ¼ 50) and in premenopausal women (HR ¼ 3.42; 95% CI, 1.08–10.85). In conclusion, we show that PTSD symptoms are associated with increased risk of ovarian cancer.

Cancer Res 2019;79:5113-20

Effect of depression before breast cancer diagnosis on mortality among postmenopausal women

Xiaoyun Liang[1], Karen L Margolis[2], Michael Hendryx[3], Katherine Reeves[4], Sylvia Wassertheil-Smoller[5], Julie Weitlauf[6,7], Suzanne C. Danhauer[8], Rowan T. Chlebowski[9], Bette Caan[10], Lihong Qi[11], Dorothy Lane[12], Sayeh Lavasani[13], and Juhua Luo[14]

BACKGROUND: Few previous studies investigating depression before the diagnosis of breast cancer and breast cancer–specific mortality have examined depression measured at more than 1 time point. This study investigated the effect of depression (combining depressive symptoms alone with antidepressant use) measured at 2 time points before the diagnosis of breast cancer on all-cause mortality and breast cancer–specific mortality among older postmenopausal women. **METHODS**: A large prospective cohort, the Women's Health Initiative, was used. The study included 3095 women with incident breast cancer who had measures of depressive symptoms and antidepressant use before their diagnosis at the baseline and at year 3. Multivariate Cox proportional hazards regression was used to estimate adjusted hazard ratios (HRs) between depression at the baseline, depression at year 3, and combinations of depression at these time points and all-cause mortality and breast cancer–specific mortality. **RESULTS**: Depression at year 3 before a breast cancer diagnosis was associated with higher all-cause mortality after adjustments for multiple covariates (HR, 1.35; 95% confidence interval [CI], 1.02-1.78. In women with late-stage (regional- or distant-stage) breast cancer, newly developed depression at year 3 was significantly associated with both all-cause mortality (HR, 2.00; 95%CI, 1.13-3.56) and breast cancer–specific mortality (HR, 2.42; 95% CI, 1.24-4.70). **CONCLUSIONS**: Women with newly developed depression before the diagnosis of breast cancer had a modestly but significantly increased risk for death from any cause and for death from breast cancer at a late stage.

Cancer. 2017 August 15; 123(16): 3107–3115. doi:10.1002/cncr.30688.

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Social isolation dysregulates endocrine and behavioral stress while increasing malignant burden of spontaneous mammary tumors

Gretchen L. Hermes[a,b], Bertha Delgado[a,c], Maria Tretiakova[a,c], Sonia A. Cavigelli[a], Thomas Krausz[a,c], Suzanne D. Conzen[a,d], and Martha K. McClintock[a,b,e,1]

[a]Institute for Mind and Biology and Departments of [b]Comparative Human Development, [c]Psychology, [d]Pathology, and [e]Medicine, The University of Chicago, Chicago, IL 60637

In a life span study, we examined how the social environment regulates naturally occurring tumor development and malignancy in genetically prone Sprague–Dawley rats. We randomly assigned this gregarious species to live either alone or in groups of five female rats. Mammary tumor burden among social isolates increased to 84 times that of age-matched controls, as did malignancy, specifically a 3.3 relative risk for ductal carcinoma in situ and invasive ductal carcinoma, the most common early breast cancers in women. Importantly, isolation did not extend ovarian function in late middle age; in fact, isolated animals were exposed to lower levels of estrogen and progesterone in the middle-age period of mammary tumor growth, with unchanged tumor estrogen and progesterone receptor status. Isolates, however, did develop significant dysregulation of corticosterone responses to everyday stressors manifest in young adulthood, months before tumor development, and persisting into old age. Among isolates, corticosterone response to an acute stressor was enhanced and recovery was markedly delayed, each associated with increased mammary tumor progression. In addition to being stressed and tumor prone, an array of behavioral measures demonstrated that socially isolated females possessed an anxious, fearful, and vigilant phenotype. Our model provides a framework for studying the interaction of social neglect with genetic risk to identify mechanisms whereby psychosocial stressors increase growth and malignancy of breast cancer.

Cancer and the Risk of Suicide in Older Americans

Matthew Miller, Helen Mogun, Deborah Azrael, Katherine Hempstead, and Daniel H. Solomon

A B S T R A C T

Purpose
To determine whether the risk of suicide is greater among patients with cancer than among patients with other medical illnesses.

Patients and Methods
A case-control study of the suicide risk associated with medical illness among older Americans that used healthcare utilization data linked to prescription and mortality files. The patient population was comprised of 1,408 New Jersey residents age 65 years or older who were enrolled in Medicare and in a pharmaceutical insurance program. Patient cases (n = 128) died as a result of suicide during the study period of 1994 to 2002. Control patients (n = 1,280) were frequency-matched to patient cases on age and sex. Data were analyzed by using the odds ratio (OR) of suicide adjusted for age, sex, ethnicity, medical and psychiatric comorbidity, and use of prescription medications.

Results
In adjusted analyses, the only medical condition that remained associated with suicide was cancer (OR, 2.3; 95% CI, 1.1 to 4.8). Suicide also remained associated with a diagnosis of affective disorder (OR, 2.3; 95% CI, 1.3 to 4.2), anxiety/personality disorder (OR, 2.2; 95% CI, 1.3 to 3.6), treatment with antidepressants (OR, 2.0; 95% CI, 1.2 to 3.2), and treatment with opioid analgesics (OR, 1.6; 95% CI, 1.0 to 2.5).

Conclusion
The risk of suicide in older adults is higher among patients with cancer than among patients with other medical illnesses, even after psychiatric illness and the risk of dying within a year were accounted for.

J Clin Oncol 26:4720-4724. © 2008 by American Society of Clinical Oncology

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JAMA Psychiatry | Original Investigation

Risk of Suicide After Cancer Diagnosis in England

Katherine E. Henson, MSc, DPhil; Rachael Brock, MB, BChir; James Charnock, MSCi; Bethany Wickramasinghe, BSc; Olivia Will, MBChB, PhD, FRCS; Alexandra Pitman, MSc(Econ), MBBS, MRCPsych, PhD

RESULTS Of the 4 722 099 patients with cancer, 50.3% were men and 49.7% were women. A total of 3 509 392 patients in the cohort (74.3%) were aged 60 years or older when the diagnosis was made. A total of 2491 patients (1719 men and 772 women) with cancer died by suicide, representing 0.08% of all deaths during the follow-up period. The overall SMR for suicide was 1.20 (95% CI, 1.16-1.25) and the AER per 10 000 person-years was 0.19 (95% CI, 0.15-0.23). The risk was highest among patients with mesothelioma, with a 4.51-fold risk corresponding to 4.20 extra deaths per 10 000 person-years. This risk was followed by pancreatic (3.89-fold), esophageal (2.65-fold), lung (2.57-fold), and stomach (2.20-fold) cancer. Suicide risk was highest in the first 6 months following cancer diagnosis (SMR, 2.74; 95% CI, 2.52-2.98).

CONCLUSIONS AND RELEVANCE Despite low absolute numbers, the elevated risk of suicide in patients with certain cancers is a concern, representing potentially preventable deaths. The increased risk in the first 6 months after diagnosis may indicate an unmet need for psychological support. The findings of this study suggest a need for improved psychological support for all patients with cancer, and attention to modifiable risk factors, such as pain, particularly in specific cancer groups.

JAMA Psychiatry. 2019;76(1):51-60. doi:10.1001/jamapsychiatry.2018.3181

Suicide Rates in Cancer Patients in the Current Era in United States

TABLE 2. Suicide Rates in Cancer Patients at Selective Sites Diagnosed During 2000–2013 in the Surveillance Epidemiology and End Results Database

Cancer Type	2000–2013 Number of Observed Suicides	2000–2013 Standardized Mortality Ratio (95% CI)	2000–2006 Standardized Mortality Ratio (95% CI)	2007–2013 Standardized Mortality Ratio (95% CI)
All sites	1,495	1.37 (1.3–1.4)	1.27 (1.2–1.5)	1.58 (1.4–1.7)
Oral cavity and pharynx	95	3.36 (2.7–4.1)	3.14 (2.4–4.1)	3.79 (2.7–5.2)
Esophagus	21	3.85 (2.4–5.9)	3.58 (1.9–5.9)	4.27 (2–8)
Stomach	20	2.50 (1.5–3.9)	2.51 (1.3–3.9)	2.49 (1–5.1)
Liver	19	3.55 (2–5.5)	3.13 (1.4–5.5)	3.92 (2–7)
Pancreas	18	3.8 (2.3–6)	2.93 (1.2–6.0)	4.72 (2.4–8.5)
Larynx	20	2.04 (1.3–3.2)	2.18 (1.2–3.2)	1.72 (0.6–4)
Lung and bronchus	137	3.37 (2.8–4)	3.3 (2.6–4)	3.48 (2.6–4.6)
Myeloma	20	2.08 (1.3–3.2)	2.56 (1.4–3.2)	1.33 (0.4–3.1)

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ARTICLE
https://doi.org/10.1038/s41467-018-08170-1 OPEN

Suicide among cancer patients

Nicholas G. Zaorsky[1,2], Ying Zhang[2], Leonard Tuanquin[1], Shirley M. Bluethmann[2], Henry S. Park[3] & Vernon M. Chinchilli[2]

Our purpose is to identify cancer patients at highest risk of suicide compared to the general population and other cancer patients. This is a retrospective, population-based study using nationally representative data from the Surveillance, Epidemiology, and End Results program, 1973-2014. Among 8,651,569 cancer patients, 13,311 committed suicide; the rate of suicide was 28.58/ 100,000-person years, and the standardized mortality ratio (SMR) of suicide was 4.44 (95% CI, 4.33, 4.55). The predominant patients who committed suicide were male (83%) and white (92%). Cancers of the lung, head and neck, testes, bladder, and Hodgkin lymphoma had the highest SMRs (> 5-10) through the follow up period. Elderly, white, unmarried males with localized disease are at highest risk vs other cancer patients. Among those diagnosed at < 50 years of age, the plurality of suicides is from hematologic and testicular tumors; if > 50, from prostate, lung, and colorectal cancer patients.

Depression and cancer mortality: a meta-analysis

M. Pinquart[1]* and P. R. Duberstein[2]

[1] *Department of Psychology, Philipps University, Marburg, Germany*
[2] *Laboratory of Personality and Development, Department of Psychiatry, University of Rochester Medical Center, Rochester, NY, USA*

Results. Depression diagnosis and higher levels of depressive symptoms predicted elevated mortality. This was true in studies that assessed depression before cancer diagnosis as well as in studies that assessed depression following cancer diagnosis. Associations between depression and mortality persisted after controlling for confounding medical variables.

Conclusions. Screening for depression should be routinely conducted in the cancer treatment setting. Referrals to mental health specialists should be considered. Research is needed on whether the treatment of depression could, beyond enhancing quality of life, extend survival of depressed cancer patients.

Psychological Medicine (2010), 40, 1797–1810

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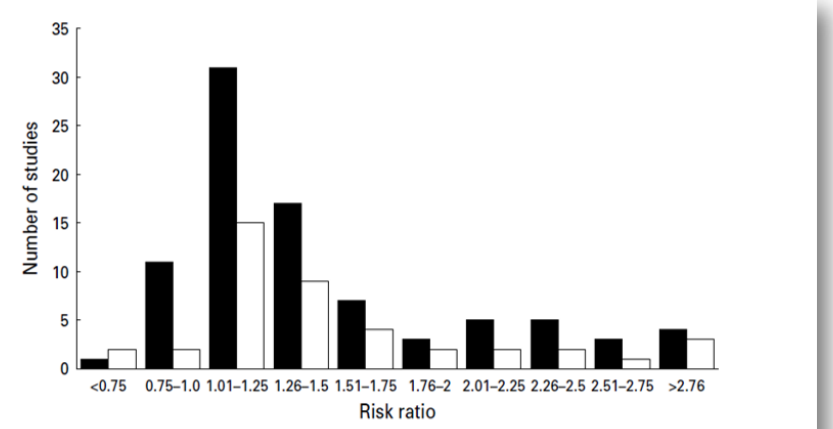

Fig. 1. Distribution of effect sizes of the individual studies. ■, Uncontrolled; □, controlled.

Psychological Medicine (2010), 40, 1797–1810

Biological Pathways

STRESS

psychological response

endocrine responses

immune function

tumor growth

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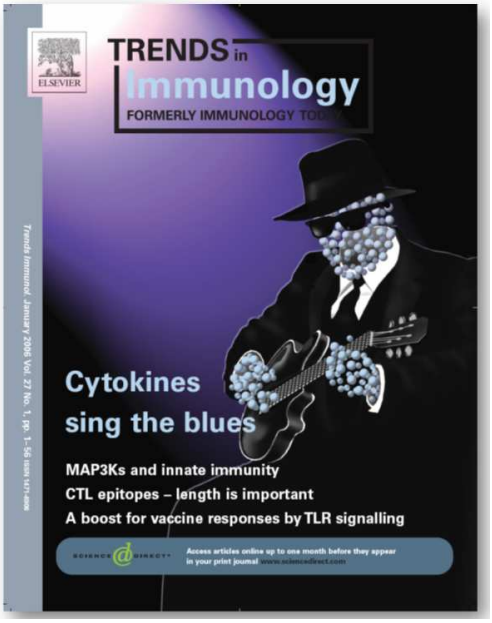
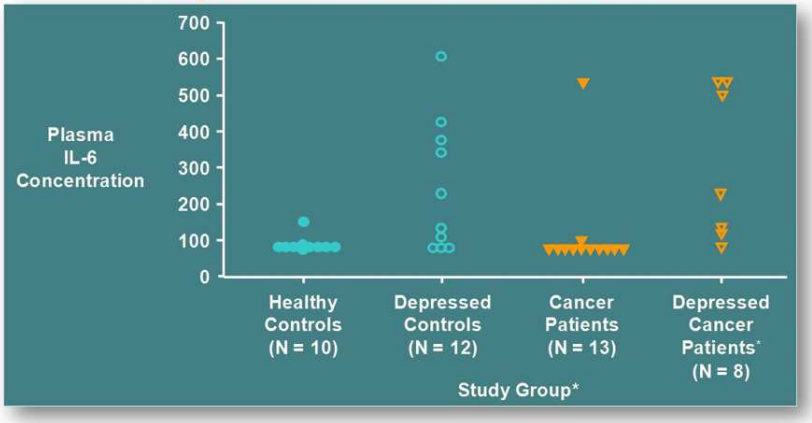


IL-6 Concentrations In Patients With Depression And Cancer



*Depressed CA Patients with highest IL-6 plasma concentrations (H = 13.9, df = 3, *P* = .003)

Musselman et al

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Basis for the Hypothesis that Inflammation may Play a Role in Depression

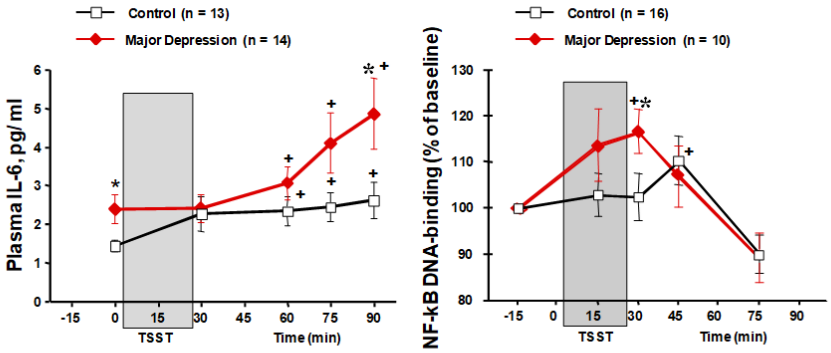
Positive correlation between depressive symptom severity and innate immune cytokines

Elevated innate immune cytokines predict poor response to antidepressant therapies and are elevated in patients with treatment resistance. Cytokine gene polymorphisms (IL-1, TNF) predict antidepressant treatment response.

Administration of innate immune cytokines (esp. IL-1, TNF-alpha, and IL-6, as well as IFN-alpha) produce behavioral changes in laboratory animals and humans that resemble major depression.

Inhibition of cytokine signaling has been found to alleviate depressive and anxiety behaviors in patients with inflammatory disorders and in laboratory animals.

Patients with Major Depression Exhibit an Exaggerated Inflammatory Response to Stress: A Possible Link Between Stress, Depression and Illness



*Between group comparison, $p < 0.05$
+Within group comparison vs. 0 min time pt, $p < 0.05$

*-the majority of the depressed patients in this sample also endorsed significant early life stress as measured by the CTQ

Pace et al., *Am J Psychiatry*, 163(9):1630-1633, 2006.

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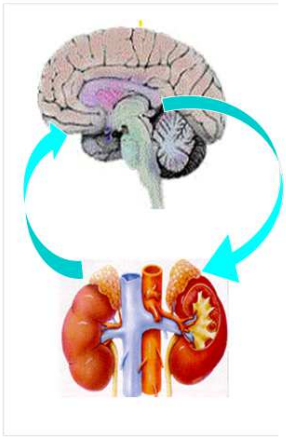
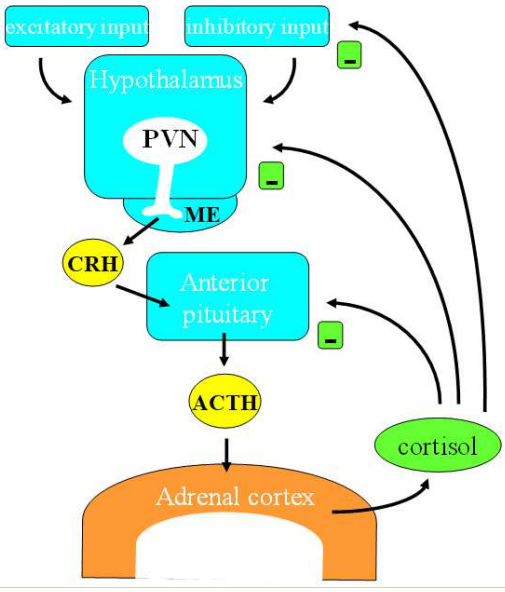
Chronic stress





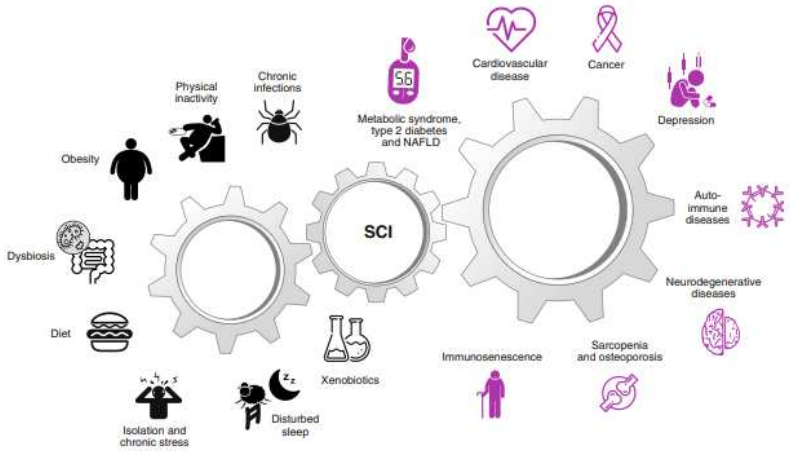


Fig. 1 | Causes and consequences of low-grade systemic chronic inflammation. Several causes of low-grade systemic chronic inflammation (SCI) and their consequences have been identified. As shown on the left, the most common triggers of SCI (in counter-clockwise direction) include chronic infections, physical inactivity, (visceral) obesity, intestinal dysbiosis, diet, social isolation, psychological stress, disturbed sleep and disrupted circadian rhythm, and exposure to xenobiotics such as air pollutants, hazardous waste products, industrial chemicals and tobacco smoking. As shown on the right, the consequences of SCI (in clockwise direction) include metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, cancer, depression, autoimmune diseases, neurodegenerative diseases, sarcopenia, osteoporosis and immunosenescence.

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Depressive Symptoms and Cortisol Rhythmicity Predict Survival in Patients with Renal Cell Carcinoma: Role of Inflammatory Signaling

Lorenzo Cohen[1]*, Steven W. Cole[2], Anil K. Sood[3], Sarah Prinsloo[1], Clemens Kirschbaum[4], Jesusa M. G. Arevalo[2], Nicholas B. Jennings[3], Shellie Scott[5], Luis Vence[6], Qi Wei[1], Diane Kentor[6], Laszlo Radvanyi[6], Nizar Tannir[7], Eric Jonasch[7], Pheroze Tamboli[8], Louis Pisters[5]

PLoS ONE 7(8): e42324, 2012

Abstract

Purpose: Evidence has supported the association between psychological factors and cancer biology; however, findings are equivocal on the role of psychosocial factors in cancer progression. This study generates a hypothesis of mechanistic variables by examining the clinical effects of psychosocial factors and cortisol dysregulation in patients with metastatic renal cell carcinoma (RCC) and examines associated activation of transcription control pathways.

Methods: Patients with metastatic RCC (n = 217) were prospectively enrolled in this study. Patients completed questionnaires (Centers for Epidemiologic Studies – Depression; SF-36 Health Status Survey; Duke Social Support Index; Coping Operations Preference Enquiry; organized and non-organized religious activity; and intrinsic religiosity), and provided blood and saliva samples. Cortisol levels and whole genome transcriptional profiling were assessed to identify potential alterations in circadian rhythms and genomic pathways.

Results: Separate Cox regression models, controlling for disease risk category, revealed that CES-D scores ($p = 0.05$, HR = 1.5, 95% CI for HR: 1.00–2.23) and cortisol slope ($p = 0.002$; HR = 1.9; 95%CI for HR: 1.27–2.97) were significantly associated with decreased survival. Only cortisol slope and risk category remained significant in the complete model. Functional genomic analyses linked depressive symptoms to increased expression of pro-inflammatory and pro-metastatic genes in circulating leukocytes. 116 transcripts were found to be upregulated by an average of 50% or more in high CES-D patients, and 57 transcripts downregulated by at least 50%. These changes were also found in the tumor in a subset of patients.

Conclusion: These findings identify depressive symptoms as a key predictor of survival in renal cell carcinoma patients with potential links to dysregulation of cortisol and inflammatory biology.

PLoS ONE 7(8): e42324, 2012

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FKBP5 polymorphisms as vulnerability to anxiety and depression in patients with advanced gastric cancer: A controlled and prospective study

Jee In Kang [a,1], Hyun Cheol Chung [b], Hei-Cheul Jeung [c], Se Joo Kim [a], Suk Kyoon An [a], Kee Namkoong [a,*]

Summary Cancer patients, who have to adapt to a long treatment process with multiple stressful events, show various stress responses. Genetic components may contribute to individual differences in stress response and risk for development of stress-related psychiatric problems. The present study aimed to investigate the influence of FK506 binding protein 5 (FKBP5) gene polymorphisms regulating the hypothalamic—pituitary—adrenal (HPA) axis on individual distress levels in cancer patients faced with similar stressful situation.

A total of 130 patients (90 males, 40 females) who were newly diagnosed with advanced gastric cancer and supposed to receive first-line chemotherapy were initially assessed, and a six-week follow-up assessment occurred for 93 patients (63 males, 30 females) after two cycles of chemotherapy. Distress levels and coping patterns were measured by the Hospital Anxiety and Depression Scale (HADS) and Mini-Mental Adjustment to Cancer (Mini-MAC) scale. For genetic factors, three single nucleotide polymorphisms of FKBP5 rs1360780, rs9296158 and rs9470080 were genotyped.

For HADS-anxiety, FKBP5 rs9296158 had a significant group-by-time interaction ($p = 0.015$), and rs9470080 and rs1360780 had a marginally significant interaction ($p = 0.023$, $p = 0.038$, respectively). For HADS-depression, rs9470080 and rs9296158 had a marginally significant group-by-time interaction ($p = 0.026$, $p = 0.032$, respectively). In addition, a step-wise linear regression analysis showed that FKBP5 rs9470080 and rs9296158 were significant predictors of anxiety and depression after prolonged stress exposure in cancer patients.

Our findings indicate that the genetic factors regulating the HPA axis such as FKBP5 gene polymorphisms may play a crucial role in anxiety and depression following prolonged stress exposure.

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Basal Cell Carcinoma

Stressful Life Events and the Tumor Environment

Christopher P. Fagundes, PhD; Ronald Glaser, PhD; Sheri L. Johnson, PhD; Rebecca R. Andridge, PhD; Eric V. Yang, PhD; Michael P. Di Gregorio, MS; Min Chen, MS; David R. Lambert, MD; Scott D. Jewell, MD; Mark A. Bechtel, MD; Dean W. Hearne, MD; Joel B. Herron, MD; Janice K. Kiecolt-Glaser, PhD

Arch Gen Psychiatry. 2012;69(6):618-626

Context: Child emotional maltreatment can result in lasting immune dysregulation that may be heightened in the context of more recent life stress. Basal cell carcinoma (BCC) is the most common skin cancer, and the immune system plays a prominent role in tumor appearance and progression.

Objective: To address associations among recent severe life events, childhood parental emotional maltreatment, depression, and messenger RNA (mRNA) coding for immune markers associated with BCC tumor progression and regression.

Design: We collected information about early parent-child experiences, severe life events in the past year as assessed by the Life Events and Difficulties Schedule, depression, and mRNA for immune markers associated with BCC tumor progression and regression from patients with BCC tumors.

Setting: University medical center.

Participants: Ninety-one patients with BCC (ages, 23-92 years) who had a previous BCC tumor.

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Main Outcome Measures: The expression of 4 BCC tumor mRNA markers (CD25, CD3ε, intercellular adhesion molecule 1, and CD68) that have been linked to BCC tumor progression and regression were assessed in BCC tumor biopsy specimens.

Results: Both maternal and paternal emotional maltreatment interacted with the occurrence of severe life events to predict the local immune response to the tumor (adjusted $P = .009$ and $P = .03$, respectively). Among BCC patients who had experienced a severe life event within the past year, those who were emotionally maltreated by their mothers ($P = .007$) or fathers ($P = .02$) as children had a poorer immune response to the BCC tumor. Emotional maltreatment was unrelated to BCC immune responses among those who did not experience a severe life event. Depressive symptoms were not associated with the local tumor immune response.

Conclusions: Troubled early parent-child relationships, in combination with a severe life event in the past year, predicted immune responses to a BCC tumor. The immunoreactivity observed in BCCs and the surrounding stroma reflects an anti–tumor-specific immune response that can be altered by stress.

Interrelationship of depression, stress and inflammation in cancer patients: A preliminary study

J.A. Archer [a], I.L. Hutchison [b], S. Dorudi [c], S.A. Stansfeld [a], A. Korszun [a,*]

[a] Queen Mary University of London, Barts and The London School of Medicine and Dentistry, Centre for Psychiatry, Wolfson Institute of Preventive Medicine, London, UK
[b] Department of Oral and Maxillofacial Surgery, Barts and The London School of Medicine and Dentistry, London, UK
[c] Centre for Digestive Diseases, Barts and The London School of Medicine and Dentistry, London, UK

ABSTRACT

Objective: Depression is common in cancer patients and detrimentally affects patients' quality of life. Both depression and stress are associated with raised inflammatory marker levels. This prospective study of cancer patients focuses on childhood trauma, recent life events and inflammatory marker levels as risk factors for high post-surgery depressive symptoms.
Methods: Ninety cancer patients (56 head and neck, 34 colorectal) completed the Hospital Anxiety and Depression Scale, pre-surgery and six, 12 and 24 weeks post-surgery. Recent life events and childhood trauma were assessed at six and 12 weeks respectively. Blood samples were taken pre- and one and six weeks post-surgery to measure C-reactive protein (CRP) and pro-inflammatory cytokine levels.
Results: Childhood trauma and recent life events were risk factors for higher depressive symptom levels. In colorectal cancer patients, baseline CRP levels were associated with depressive symptom levels at six ($p=0.008$) and 12 weeks ($p=0.038$). Baseline and six week Tumour Necrosis Factor-alpha (TNFα) levels were significantly associated with higher depressive symptoms at later time points after adjusting for cancer-related variables. Childhood trauma was positively associated with TNFα and CRP levels in colorectal cancer patients. The associations between inflammatory markers and depressive symptoms were not significant after adjusting for childhood trauma.
Limitations: Small sample size.
Conclusions: Raised inflammatory mediator levels may be risk factors for depressive symptoms in colorectal cancer patients and thus worth considering as a potential therapeutic target. These pilot data support recent findings demonstrating long-term effects of childhood adversity on adult health.

Journal of Affective Disorders 143 (2012) 39–46

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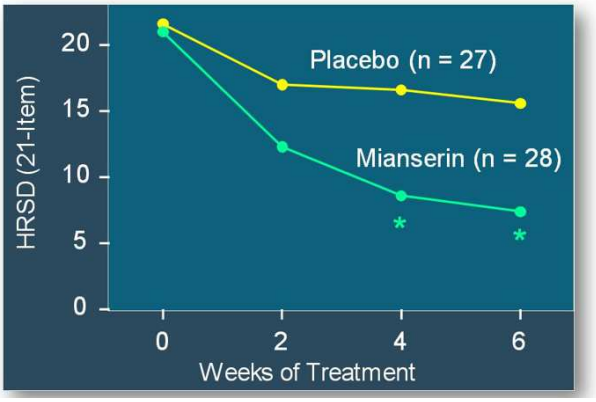
Treatment of Depression in Breast Cancer Patients (Stages I and II): *Mianserin vs Placebo*



* $P < .05$, 60 mg vs placebo.
HRSD = Hamilton Rating Scale for Depression.
van Heeringen K, Zivkov M. *Br J Psychiatry.* 1996;169:440-443.

Adherence to antidepressant medications is associated with reduced premature mortality in patients with cancer: A nationwide cohort study

Gal Shoval[1,2,3] | Ran D. Balicer[1,4] | Becca Feldman[1] | Moshe Hoshen[1] | Gilad Eger[2,3] | Abraham Weizman[2,3,5] | Gil Zalsman[2,3,5,6] | Brendon Stubbs[7] | Pavel Golubchik[2,3] | Barak Gordon[8,9] | Amir Krivoy[1,2,3,7]

Depress Anxiety. 2019;36:921-929.

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Abstract

Background: Depression and anxiety are common in cancer and antidepressants (AD) are efficacious treatment. The relationship between AD adherence and mortality in cancer is unclear. This study aimed to evaluate the association between adherence to AD and all-cause mortality in a population-based cohort of patients with cancer.

Materials and Methods: We conducted a 4-year historical prospective cohort study including 42,075 patients with cancer who purchased AD at least once during the study period. Adherence to AD was modeled as nonadherence (<20%), poor (20–50%), moderate (50–80%), and good (>80%) adherence. We conducted multivariable survival analyses adjusted for demographic and clinical variables that may affect mortality.

Results: During 1,051,489 person-years at risk follow-up, the adjusted hazard ratios (HR) for mortality were 0.89 (95% confidence interval [CI]: 0.83–0.95), 0.77 (95% CI: 0.66–0.72), and 0.80 (95% CI: 0.76–0.85) for the poor, moderate, and good adherence groups, respectively, compared to the nonadherent group. Analysis of the entire sample and a subgroup with depression, for cancer subtypes, revealed similar patterns for breast, colon, lung, and prostate cancers, but not for melanoma patients. Multivariate predictors of premature mortality included male gender (HR 1.48 [95% CI: 1.42–1.55]), current/past smoking status (HR 1.1, [95% CI: 1.04–1.15]; $P < .0001$), low socioeconomic status (HR 1.1, [95% CI: 1.03–1.17]; $P < .0001$) and more physical comorbidities.

Conclusions: The present study is the first to demonstrate that higher adherence to AD is associated with a decrease of all-cause mortality in a large nationwide cohort of cancer patients. Our data add to the pressing need to encourage adherence to AD among cancer patients.

Let no one persuade you to cure the headache until he has given you his soul to be cured. For this is the great error of our day in the treatment of the human body, that physicians separate the soul from the body.

--Hippocrates 2000BC

NOTHING VIVIFIES AND NOTHING KILLS LIKE THE EMOTIONS.

--Joseph Roux 1886

"Grief is Mortal… that is to say deadly"

— Shakespeare (1599)

Every affectation of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart.

--William Harvey 1628

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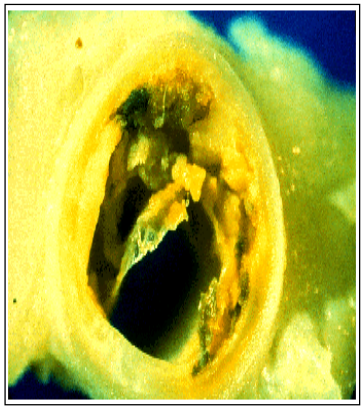
Depression And Cardiovascular Disease

- ↑ rate of depression in ischemic heart disease (IHD)
- Depression is a risk factor for morbidity/mortality post-MI
- Depression is a risk factor for development of coronary artery disease
- Depression associated with increased platelet activation, platelet reactivity, cardiac events
- SSRIs effective antidepressants in IHD without adverse effects of TCAs

Previously Identified Risk Factors for Coronary Artery Disease

- Genetic Factors
- Diabetes
- Hypertension
- Thrombocyte Dysfunction
- Hyperlipidemia
- Smoking
- Obesity



Photograph: Davies MJ.
Circulation 94:2013-2020, 1996

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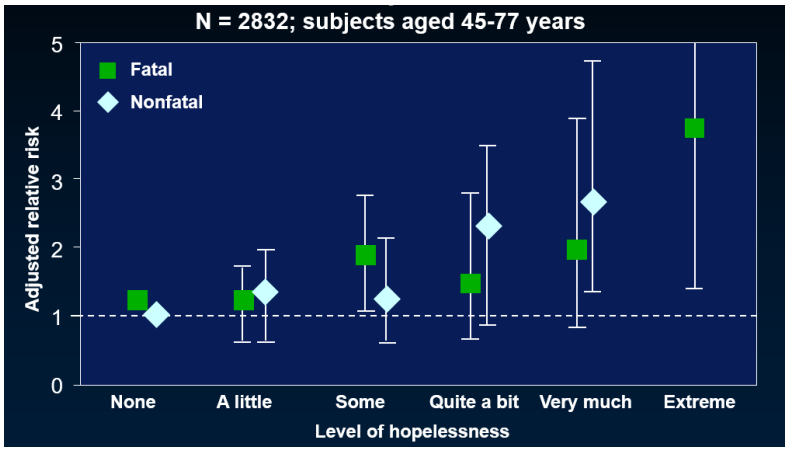
Relationship Between Depression and Ischemic Heart Disease (IHD)

- 2,832 participants in the National Health Examination Follow-up study
  - Ages 45-77 with no IHD
- Baseline assessment with General Well-Being Schedule
  - Depressed affect 11.5%
  - Moderate hopelessness 10.8%
  - Severe hopelessness 2.9%
- Follow-up
  - Mean 12.4 years
  - 189 cases of fatal IHD
- Depressed affect and hopelessness were associated with fatal and non-fatal IHD

Anda et al., *Epidemiology 4:285, 1993*

Fatal and Nonfatal Ischemic Heart Disease (IHD) over 12.4 Years' Follow-up



Anda et al. *Epidemiology.* 1993;4:285-294.

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Depression Following Myocardial Infarction

Impact on 6-Month Survival

Nancy Frasure-Smith, PhD; François Lespérance, MD; Mario Talajic, MD

JAMA. 1993;270(15):1819-1825. doi:10.1001/jama.1993.03510150053029

Mortality and Depression Post-MI

N = 222 post-MI

↓ 7 days post MI

Interview and DIS performed to determine if DSM-III-R criteria met

↓ 6 months f/u

Determination of survival

Frasure-Smith et al., *JAMA* 270:1819-1825, 1993

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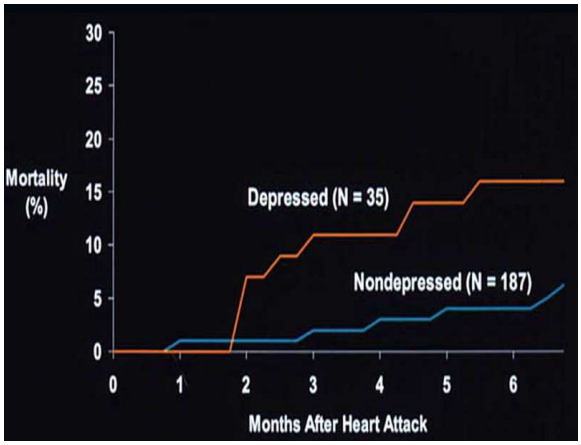
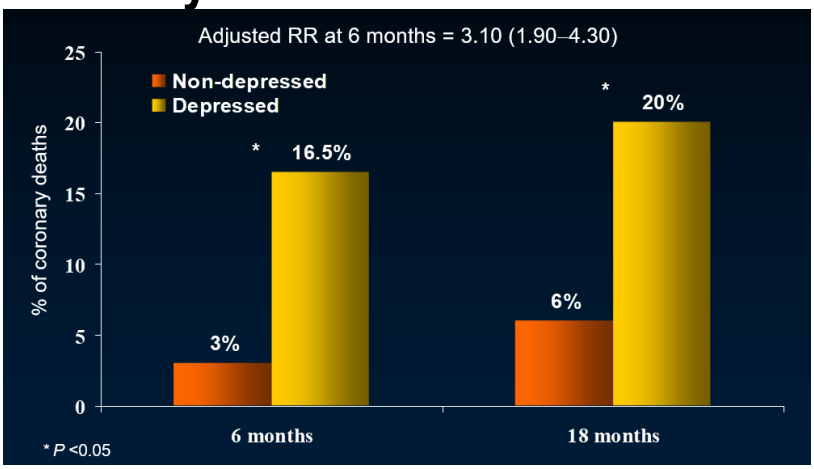
Cumulative Mortality for Depressed and Nondepressed Patients Following Heart Attack



Frasure-Smith et al., *JAMA* 270:1819-1825, 1993

6-Month and 18-Month Coronary Fatalities After Acute MI



Frasure-Smith et al., *JAMA* 270(15):1819–1825, 1993
Frasure-Smith et al., *Circulation* 91:999–1005, 1995

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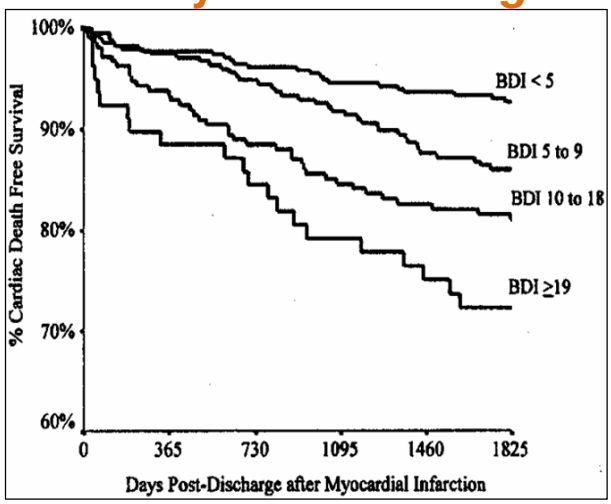
Long-term survival after MI in relation to Beck Depression Inventory Score during hospitalization



Lespérance et al., *Circulation* 105: 1049-1053, 2002

Depression as a risk factor for mortality after coronary artery bypass surgery

*James A Blumenthal, Heather S Lett, Michael A Babyak, William White, Peter K Smith, Daniel B Mark, Robert Jones, Joseph P Mathew, Mark F Newman, for the NORG Investigators**

Lancet 2003; **362:** 604–09

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Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease.

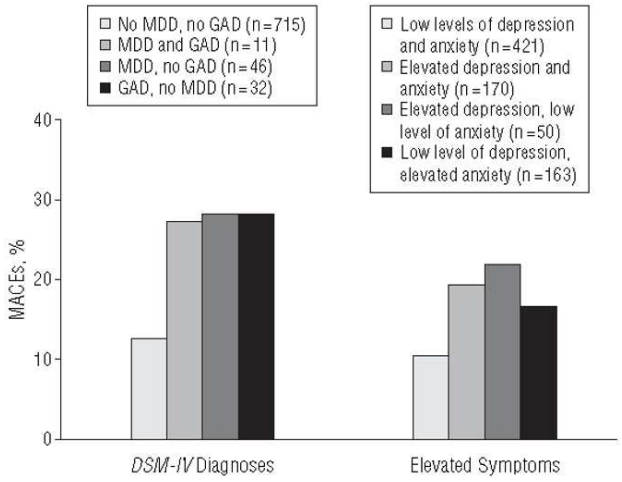
Frasure-Smith N[1], Lespérance F.

DESIGN, SETTING, AND PATIENTS: Two-year follow-up of 804 patients with stable CAD (649 men) assessed using the Beck Depression Inventory II (BDI-II), the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A), and the Structured Clinical Interview for DSM-IV (masked to self-reports) 2 months after acute coronary syndromes.

MAIN OUTCOME MEASURES: Major adverse cardiac events (MACEs) (cardiac death, myocardial infarction, cardiac arrest, or nonelective revascularization) in the 2 years after baseline.

Arch Gen Psychiatry. 2008 Jan;65(1):62-71. doi: 10.1001/archgenpsychiatry.2007.4.

Depression and Anxiety as Predictors of 2-Year Cardiac Events in Patients With Stable Coronary Artery Disease



Frasure-Smith and Lesperance (2008) *Arch Gen Psychiatry* 65:62-71.

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Change in Depression as a Precursor of Cardiovascular Events

Sylvia Wassertheil-Smoller, PhD; William B. Applegate, MD; Kenneth Berge, MD; Chee Jen Chang, PhD; Barry R. Davis, MD, PhD; Richard Grimm Jr, MD, PhD; John Kostis, MD; Sara Pressel, MS; Eleanor Schron, RN, MS

Arch Intern Med. 1996;156(5):553-561. doi:10.1001/archinte.1996.00440050111012

Objective: To determine the relationship between increasing depressive symptoms and cardiovascular events or mortality.

Design: Cohort analytic study of data from randomized placebo-controlled double-blind clinical trial of antihypertensive therapy. Depressive symptoms were assessed semiannually with the Center for Epidemiological Studies– Depression (CES-D) scale during an average follow-up of 4.5 years.

Setting: Ambulatory patients in 16 clinical centers of the Systolic Hypertension in the Elderly Program.

Patients: Generally healthy men and women aged 60 years or older randomized to active antihypertensive drug therapy or placebo who were 79% white and 53% women and had follow-up CES-D scores and no outcome events during the first 6 months (N=4367).

Main Outcome Measures: All-cause mortality, fatal or nonfatal stroke, or myocardial infarction. Results: Baseline depressive symptoms were not related to subsequent events; however, an increase in depression was prognostic. Cox proportional hazards regression analyses with the CES-D scale as a time-dependent variable, controlling for multiple covariates, indicated a 25% increased risk of death per 5-unit increase in the CES-D score (relative risk [RR], 1.25; 95% confidence interval [CI], 1.15 to 1.36). The RR for stroke or myocardial infarction was 1.18 (95% CI, 1.08 to 1.30). Increase in CES-D score was an independent predictor in both placebo and active drug groups, and it was strongest as a risk factor for stroke among women (RR, 1.29; 95% CI, 1.07 to 1.34).

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- Conclusions: Among elderly persons, a significant and substantial excess risk of death and stroke or myocardial infarction was associated with an increase in depressive symptoms over time, which may be a marker for subsequent major disease events and warrants the attention of physicians to such mood changes. However, further studies of causal pathways are needed before widespread screening for depression in clinical practice is to be recommended.

Depression Is a Risk Factor for Coronary Artery Disease in Men

The Precursors Study

Daniel E. Ford, MD, MPH; Lucy A. Mead, ScM; Patricia P. Chang, MD; Lisa Cooper-Patrick, MD, MPH; Nae-Yuh Wang, MS; Michael J. Klag, MD, MPH

Arch Intern Med. 1998;158:1422-1426

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Background: Several studies have found that depression is an independent predictor of poor outcome after the onset of clinical coronary artery disease. There are few data concerning depression as a risk factor for the development of coronary artery disease.

Objective: To determine if clinical depression is an independent risk factor for incident coronary artery disease.

Patients and Methods: The Johns Hopkins Precursors Study is a prospective, observational study of 1190 male medical students who were enrolled between 1948 and 1964 and who continued to be followed up. In medical school and through the follow-up period, information was collected on family history, health behaviors, and clinical depression. Cardiovascular disease end points have been assessed with reviews of annual questionnaires, National Death Index searches, medical records, death certificates, and autopsy reports.

Arch Intern Med. 1998;158:1422-1426

Results: The cumulative incidence of clinical depression in the medical students at 40 years of follow-up was 12%. Men who developed clinical depression drank more coffee than those who did not but did not differ in terms of baseline blood pressure, serum cholesterol levels, smoking status, physical activity, obesity, or family history of coronary artery disease. In multivariate analysis, the men who reported clinical depression were at significantly greater risk for subsequent coronary heart disease (relative risk [RR], 2.12; 95% confidence interval [CI], 1.24-3.63) and myocardial infarction (RR, 2.12; 95% CI, 1.11-4.06). The increased risk associated with clinical depression was present even for myocardial infarctions occurring 10 years after the onset of the first depressive episode (RR, 2.1; 95% CI, 1.1-4.0).

Conclusion: Clinical depression appears to be an independent risk factor for incident coronary artery disease for several decades after the onset of the clinical depression.

Arch Intern Med. 1998;158:1422-1426

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Depression Predicts Mortality Following Cardiac Valve Surgery

P. Michael Ho, MD, Frederick A. Masoudi, MD, MSPH, John A. Spertus, MD, MPH, Pamela N. Peterson, MD, A. Laurie Shroyer, PhD, Martin McCarthy, Jr, PhD, Frederick L. Grover, MD, Karl E. Hammermeister, MD, and John S. Rumsfeld, MD, PhD

(Ann Thorac Surg 2005;79:1255–9)

Insights Into Causal Pathways for Ischemic Heart Disease

Adverse Childhood Experiences Study

Maxia Dong, MD, PhD; Wayne H. Giles, MD, MS; Vincent J. Felitti, MD; Shanta R. Dube, MPH; Janice E. Williams, PhD; Daniel P. Chapman, PhD; Robert F. Anda, MD, MS

(*Circulation*. 2004;110:1761-1766.)

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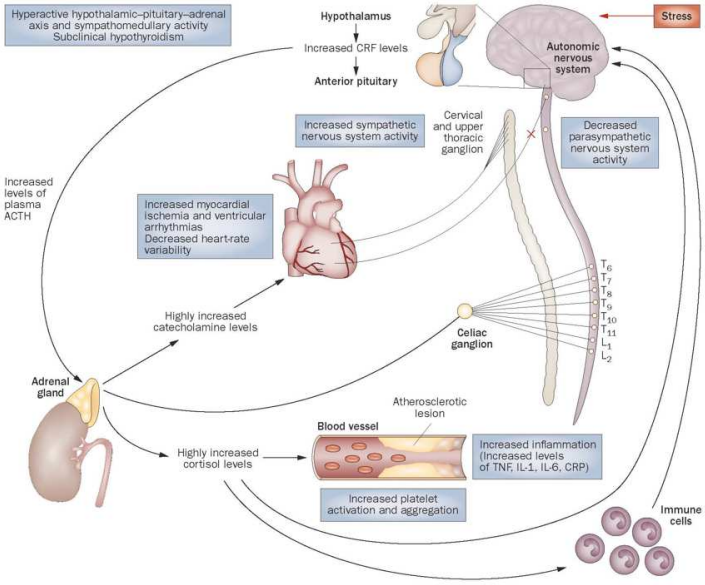
Background—The purpose of this study was to assess the relation of adverse childhood experiences (ACEs), including abuse, neglect, and household dysfunction, to the risk of ischemic heart disease (IHD) and to examine the mediating impact on this relation of both traditional IHD risk factors and psychological factors that are associated with ACEs.

Methods and Results—Retrospective cohort survey data were collected from 17 337 adult health plan members from 1995 to 1997. Logistic regression adjusted for age, sex, race, and education was used to estimate the strength of the ACE–IHD relation and the mediating impact of IHD risk factors in this relation. Nine of 10 categories of ACEs significantly increased the risk of IHD by 1.3- to 1.7-fold versus persons with no ACEs. The adjusted odds ratios for IHD among persons with ≥7 ACEs was 3.6 (95% CI, 2.4 to 5.3). The ACE–IHD relation was mediated more strongly by individual psychological risk factors commonly associated with ACEs than by traditional IHD risk factors. We observed significant association between increased likelihood of reported IHD (adjusted ORs) and depressed affect (2.1, 1.9 to 2.4) and anger (2.5, 2.1 to 3.0) as well as traditional risk factors (smoking, physical inactivity, obesity, diabetes and hypertension), with ORs ranging from 1.2 to 2.7.

Conclusions—We found a dose-response relation of ACEs to IHD and a relation between almost all individual ACEs and IHD. Psychological factors appear to be more important than traditional risk factors in mediating the relation of ACEs to the risk of IHD. These findings provide further insights into the potential pathways by which stressful childhood experiences may increase the risk of IHD in adulthood. **(*Circulation*. 2004;110:1761-1766.)**



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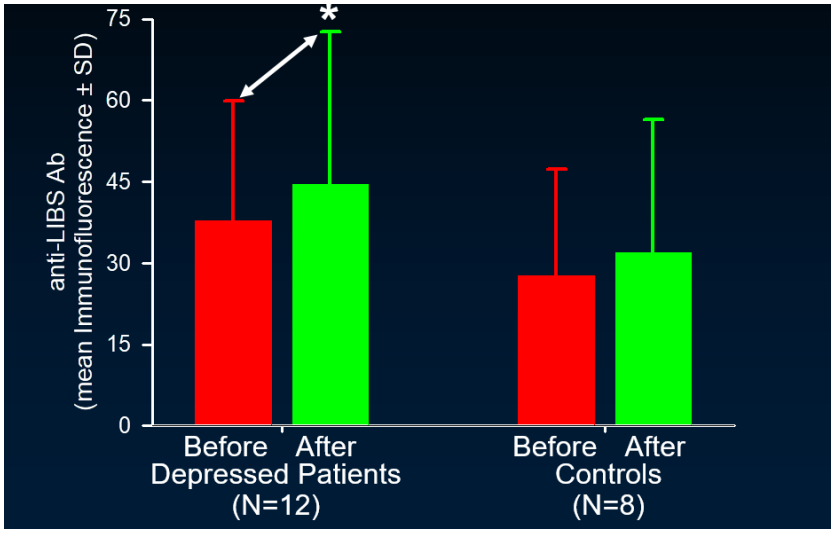
Exaggerated platelet reactivity in major depression.

Musselman DL[1], Tomer A, Manatunga AK, Knight BT, Porter MR, Kasey S, Marzec U, Harker LA, Nemeroff CB.

Am J Psychiatry. 1996 Oct;153(10):1313-7.

Exaggerated Platelet Reactivity in Major Depression Before and After Orthostatic Challenge



Musselman et al., Am J Psychiatry 153: 1313-1317, 1996

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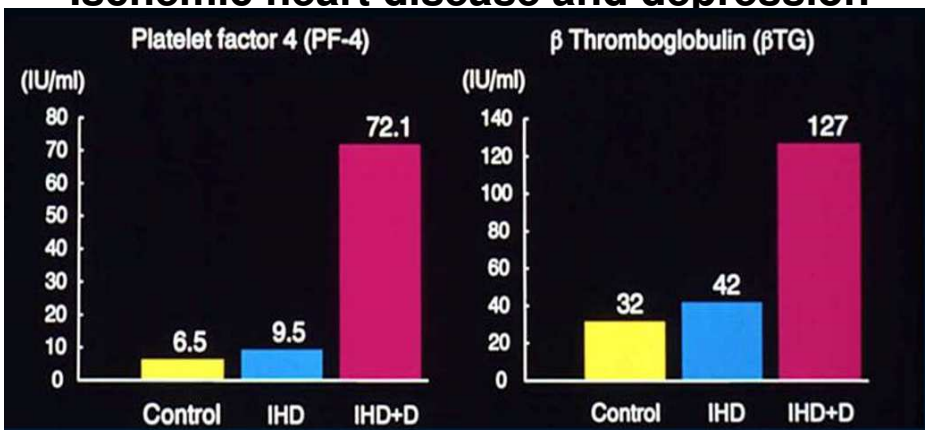
Platelet Activation
Ischemic heart disease and depression



IHD = ischemic heart disease; D = depression.

Biol Psychiatry 42: 290-295, 1997

Antidepressant may block heart attacks

Zoloft alleviates sticky situation in blood

USA TODAY – WEDNESDAY, MARCH 17, 1999

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Association of Depression With Reduced Heart Rate Variability in Coronary Artery Disease

Robert M. Carney, PhD, Roger D. Saunders, PhD, Kenneth E. Freedland, PhD, Phyllis Stein, PhD, Michael W. Rich, MD, and Allan S. Jaffe, MD

Am J Cardiol 1995;76:562–564

Sertraline Treatment of Major Depression in Patients With Acute MI or Unstable Angina

SADHART Principal Investigators

Brian Baker, MD; David Barton, MD; Bradley Bart, MD; Peter Berman, MD; David Brewer, MD; Kevin Browne, MD; John Burks, MD; Robert Campagna, MD; Peter Clemmensen, MD; David Colquhoun, MD; Clinton Corder, MD; Eric Eichhorn, MD; Mitchell Finkel, MD; Les Forman. MD; Andrew Gaffney, MD; Alexander Glassman, MD; David Goldberg, MD; Veeraindar Goli, MD; Wayne Goodman, MD; Richard Gray, MD; John Griffin, MD; Torben Haghfelt, MD; Mark Kelemen, MD; Helmut Klein, MD; Michael Koren, MD; Charles Landau, MD; Lidia Lidagoster,MD; Frank McGrew, MD; Andre Natale, MD; Frank Navetta, MD; Charles Nemeroff, MD; Gerard O'Donnell, MD; Sebastian Palmeri, MD; Kevin Rapepport, MD; David Sane, MD; Peter Schwartz, MD; Dennis Sprecher, MD; Joshua Straus, MD; J. Robert Swenson, MD; Karl Swedberg, MD; Louis Van Zyl, MD; Richard Veith, MD; William Wainwright, MD; Richard Weisler, MD; Tom Wise, MD

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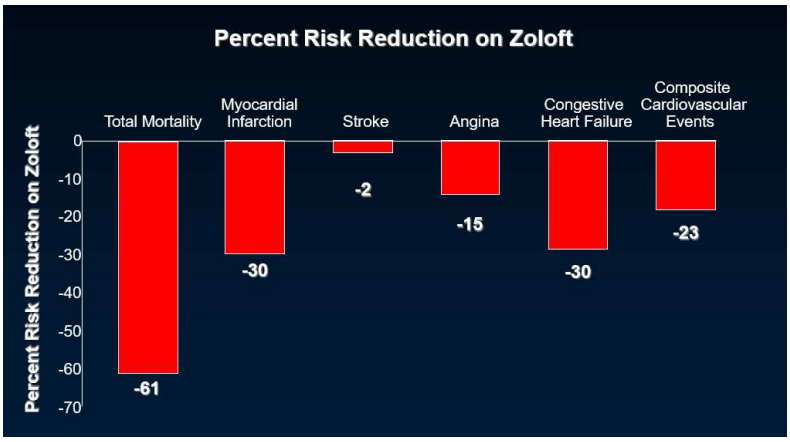
Risk of Serious Cardiovascular Events



Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction.

Taylor CB[1], Youngblood ME, Catellier D, Veith RC, Carney RM, Burg MM, Kaufmann PG, Shuster J, Mellman T, Blumenthal JA, Krishnan R, Jaffe AS; ENRICHD Investigators.

Arch Gen Psychiatry. 2005 Jul;62(7):792-8.

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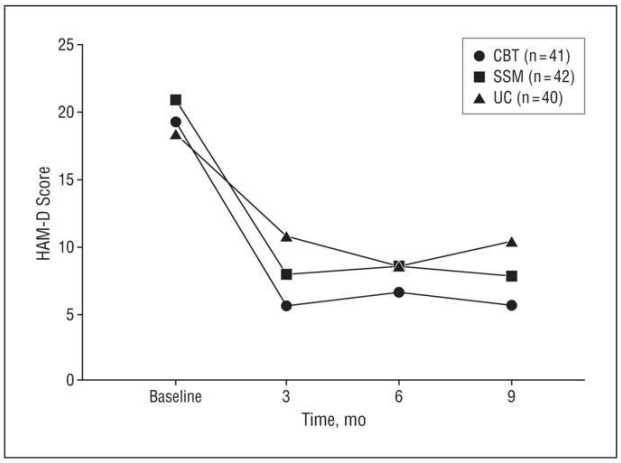
Cognitive behavior therapy and supportive stress management are efficacious for treating depression after coronary artery bypass surgery, relative to usual care.

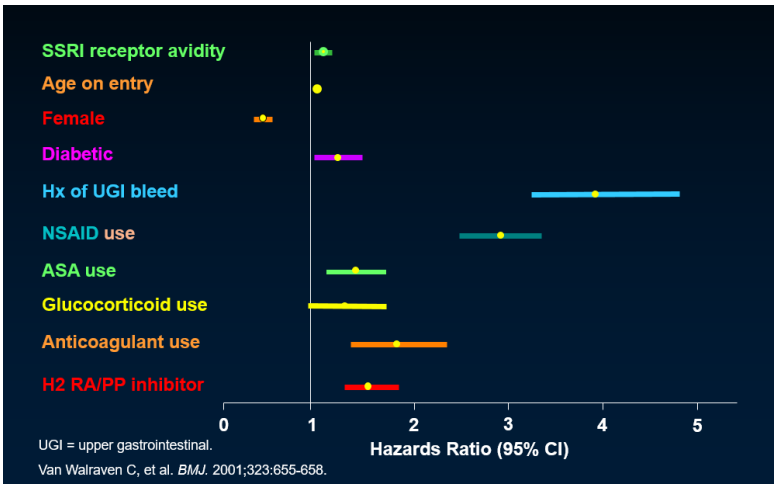


CBT had greater and more durable effects than SSM on depression and several secondary psychological outcomes.

Freedland et al (2009) Arch Gen Psychiatry 66:387-396.

Cognitive Behavior Therapy (CBT), Supportive Stress Management (SSM), Usual Care (UC).

UGI Bleeding: Risk of SSRIs Compared With Others



UGI = upper gastrointestinal.

Van Walraven C, et al. *BMJ.* 2001;323:655-658.

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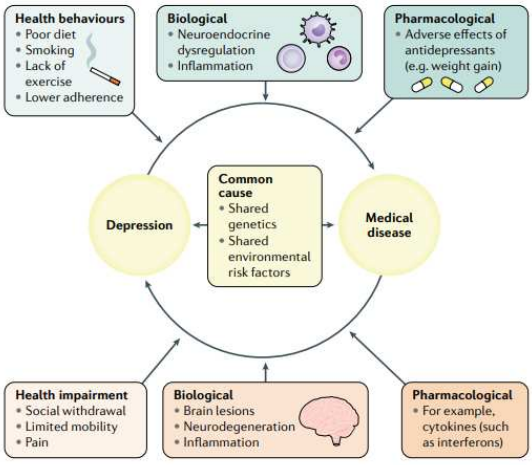

Fig. 3 | **Aetiopathogenesis of comorbid depression.** Shared genetic or environmental risk factors may contribute to comorbid depression in those with medical diseases. The link between depression and medical diseases could be enhanced via a bidirectional feedforward loop that includes behavioural, biological and pharmacological factors.

Gold, S.M., Köhler-Forsberg, O., Moss-Morris, R. *et al.* Comorbid depression in medical diseases. *Nat Rev Dis Primers* **6**, 69 (2020). https://doi.org/10.1038/s41572-020-0200-2

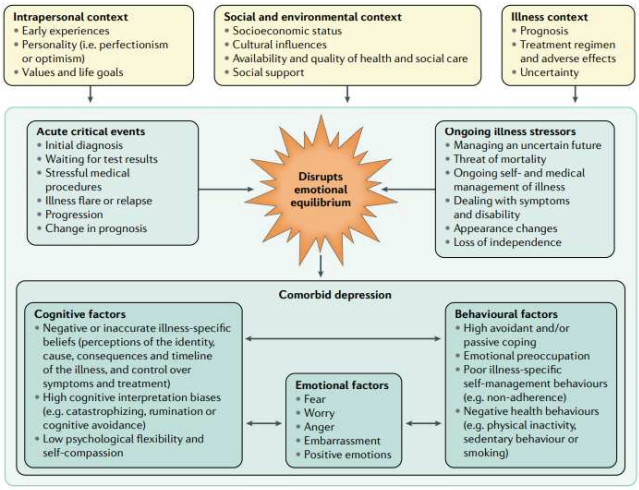

Fig. 4 | **Psychological factors involved in adjusting to chronic illness.** Intrapersonal, social, environmental and illness-related factors can contribute to depression directly and indirectly through cognitive, behavioural and emotional responses to the illness. Adapted with permission from REF.[111], Wiley.

Gold, S.M., Köhler-Forsberg, O., Moss-Morris, R. *et al.* Comorbid depression in medical diseases. *Nat Rev Dis Primers* **6**, 69 (2020). https://doi.org/10.1038/s41572-020-0200-2

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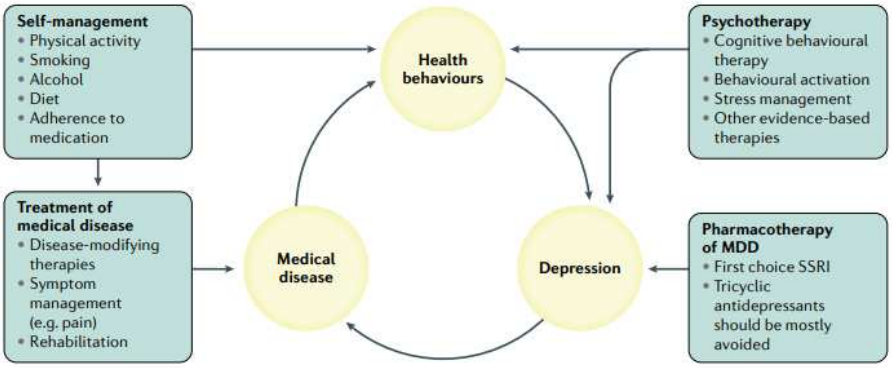

Fig. 6 | **Interdisciplinary care for comorbid depression.** Treatment of depression in people with medical diseases consists of four pillars (self-management, psychotherapy, treatment of the medical disease and pharmacotherapy of major depressive disorder (MDD)) that ideally should be combined in interdisciplinary, comprehensive care. In terms of psychotherapy, cognitive behavioural therapy has the most supporting evidence. The potential benefits and harm of the medication need to be weighed carefully for pharmacotherapy of both MDD and the medical disease (see BOX 4). Additional important aspects include the thorough treatment of the comorbid medical disease and modification of behaviours that might additionally elicit antidepressive effects or reduce risk factors such as smoking cessation, increasing physical activity and improving diet. SSRI, serotonin reuptake inhibitor.

Gold, S.M., Köhler-Forsberg, O., Moss-Morris, R. *et al.* Comorbid depression in medical diseases. *Nat Rev Dis Primers* **6**, 69 (2020). https://doi.org/10.1038/s41572-020-0200-2

Box 5 | Depression and pain

Pain is a very common symptom in many medical diseases across all disciplines, including cancer[289], rheumatoid arthritis[121], inflammatory bowel disease[290], type 2 diabetes mellitus[291] and Parkinson disease[292]. Indeed, one meta-analysis found that 39% of patients with cancer reported pain after curative treatment, 55% of patients reported pain during anticancer treatment and 66% of patients with advanced, metastatic or terminal disease reported pain. Importantly, moderate to severe pain was reported by 38% of all patients[289].

Unsurprisingly, pain is a very strong predictor of depression and vice versa. Among many other examples, the presence of pain is associated with a 2.5–10-fold increased risk of comorbid depression[293] in primary care cross-sectionally, with a 2–4-fold increased risk of newly developing depression over 4 years[294]. Importantly, one meta-analysis of studies from low-income and middle-income countries confirmed very high comorbidity rates, finding a prevalence of 34% for severe pain in patients with major depressive disorder[295]. Furthermore, pain is a strong predictor for non-remission during antidepressive treatment[296] and for recurrence of depressive episodes (as opposed to the medical illness itself[297]).

Thus, the successful treatment of pain is essential to successfully treat depression (and vice versa). In other words, antidepressive treatment is pain treatment that, in turn, is antidepressive treatment. As a general rule, serotonin–noradrenaline reuptake inhibitors and cognitive behavioural therapy have been effective in treatment of both pain and depression and are, therefore, recommended in many guidelines[295,298].

Gold, S.M., Köhler-Forsberg, O., Moss-Morris, R. *et al.* Comorbid depression in medical diseases. *Nat Rev Dis Primers* **6**, 69 (2020). https://doi.org/10.1038/s41572-020-0200-2