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Depressed mood and cause-specific mortality: a 40-year general community assessment

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Abstract

Purpose—The current study describes how the excess mortality risk associated with depression translates into specific causes of death occurring during a 40-year follow-up period, with focus on deaths related to injuries, cardiovascular diseases, and cancer.

Methods—Data comes from a cross-sectional survey (Community Mental Health Epidemiology Study) conducted in the early 1970s in Washington County, Maryland. Random sampling for the survey resulted in 2762 interviews. For the current analyses, baseline depressed mood was linked to current participant vital status through the use of death certificate records.

Results—The relative subdistribution hazards for cardiovascular deaths (3.08 (1.74–5.45)) and fatal injuries (4.63 (1.76–12.18)) were significant over the entire 40-year period for young adults (18–39 years old at baseline). The relative subdistribution hazard for cardiovascular deaths during the first 15 years of follow-up was pronounced in elderly (≥ 65 years) males (2.99 (1.67–5.37)). There were no significant associations between depressed mood and cancer deaths.

Conclusions—Individuals in the general community with depressed mood may be at increased risk of deaths due to cardiovascular disease and injury, even several decades after exposure assessment. Young adults with depressed mood appear to be particularly vulnerable to these associations.

MeSH Headings

Depression; depressive symptoms; death; mortality; cardiovascular diseases; wounds and injury

Introduction

The association between depression and elevated total mortality risk in the general community is becoming established. A 2002 meta-analysis of 25 community studies placed the overall relative risk estimate at 1.81 (95% CI: 1.58–2.07) (1). Few studies in the general

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community have simultaneously addressed total mortality assessments with broad cause of death assessments.

Prior studies have often focused on the association between depression and the development of specific diseases and survival from that same disease. A consistent finding in prior literature has been the association between depression and the development and progression of cardiovascular disease in otherwise healthy individuals (2–6). Some studies have also indicated an association between depression and increased cardiovascular mortality in populations with pre-existing disease (7).

The association between depression and the development of cancer is less established. Findings have indicated an increased risk (8) in the absence of smoking, increased risk only in the presence of smoking (9, 10) or lack of any major evidence (11–13). Some studies have linked depressive symptoms to survival from liver cancer (14), breast cancer (15) and multiple tissue sites (16, 17). Broader assessments of depressive symptoms and psychological coping mechanisms have found no association with survival from cancer (18).

Findings are mixed, but potential associations with fatal injuries beyond the association with suicide may exist. Participants with depression in general community populations have been found to be at increased risk of falls (19, 20), becoming a homicide victim (21), motor vehicle accidents (22), and non-suicidal self-injurious behavior (23, 24). More extensive injury research has been performed in older adult populations where evidence of an association is more lacking. Findings have suggested that depression in unrelated to fracture risks (25), motor vehicle collisions (26), or injury severity (27) in older adults.

Studies also suggest that the major causes of death are similar between individuals with and without depression. Cardiovascular disease, respiratory disease, and cancer formed the majority of deaths in a Dutch population comprised of older adults aged 55–85 years, regardless of depression status (28). Similar findings were reported in a study of participants 25 years and older in the United States (29). Although injury deaths were reported in these prior studies, they constituted only a small proportion of the total mortality in both exposure groups.

The association between depression and excess risk of death does not appear to be readily explained by one cause of death. General community studies have indicated depression may be simultaneously linked to excess risk of death across a variety of causes. A study of the elderly in Japan over a 15-year follow-up period found associations between baseline depression and excess mortality risk due to cerebrovascular diseases, cancer, respiratory disorders, and suicide (30). A study of middle-aged adults in the Netherlands also found associations with multiple causes of death including cardiovascular disease, cancer, and accidents during an approximate 5-year follow-up interval (31).

Given studies involving older adults predominate the field, whether depression in young adulthood can be linked to specific causes of death throughout the life span remains underexplored. The current study examines causes of death associated with depressed mood in a general community study from Washington County, Maryland, involving a 40-year follow-up period. The four-decade period allows tracking of cause-specific mortality risk through the entire adult life course for young adults at baseline. The current study examines whether expanding the public health burden of depression is warranted given its potential impact on the mortality experience of young adults in the general community.

Methods

Study population overview

Data for this study comes from the revival of a cross-sectional survey (Community Mental Health Epidemiology Study (CMHE)) conducted in the early 1970s in Washington County, Maryland (32). The purpose of the CMHE was to characterize mood symptomatology in the general population. Interviewing began in December 1971 and continued until July 1974.

Sampling for the CMHE occurred through a 98% complete household roster from a private county census conducted in 1963 (33). Households were randomly selected from the listing and samples were stratified by geographic location and socioeconomic status. One individual in each selected household ≥18 years was then randomly selected for interview. The sampling resulted in 2762 interviews forming a 78% response rate.

Exposure measurement: depressed mood

The CMHE contained the first use of the CES-D Scale (32, 34). A score ≥16 was used in this analysis to indicate the presence of depressed mood. This cut-off point was developed from CMHE data (32).

Outcome measurement: mortality linkage

Baseline depressive symptoms from the cross-sectional CMHE study were linked to mortality status over 40 years through the use of three main mortality sources. First, Washington County death certificates were searched for deaths occurring 1972–2011. Second, participants who were not found deceased using county records were then submitted to the National Death Index. NDI records were searched for deaths occurring 1979–2008 (all available NDI dates). Third, the Social Security Death Index (SSDI) was used to locate evidence of death for recent participant deaths (deaths occurring March 2011–August 2011). Participants for whom no death record was located using the three sources were then assumed to be alive as of August 1, 2011. The Johns Hopkins Bloomberg School of Public Health Institutional Review Board approved the mortality linkage and related analyses.

Outcome measurement: cause of death determination

All cause of death information came from the underlying cause of death listed on the death certificate. Complete cause of death information was available on 1477 (95.5%) of all participants determined to be deceased. Cause of death information was available as a single *International Classification of Disease* (ICD) code for the underlying cause of death. The obtained ICD codes were from the *Eighth* (35), *Ninth* (36), and *Tenth* (37) *Revisions* of the ICD.

Broad categories were created to reflect related causes of death (i.e. cardiovascular disease (diseases of the heart, cerebrovascular diseases, essential hypertension and hypertensive renal diseases), cancer (any malignant neoplasm), and fatal injuries (accidents (unintentional injuries), intentional self-harm (suicide), and assault (homicide)) based on U.S. National Vital Statistics Reports (38). All other causes of death besides cardiovascular, cancer, and fatal injuries were categorized as “other causes of death”.

Covariate assessment

Baseline age in years and sex were the main covariates of interest for this study. Baseline smoking status (ever versus never), years of education (categorized as at least high school or less than high school), and healthy body weight (measured by body mass index categories

with 18.5–24.9 representing the healthy BMI range using baseline self-reported weight and height) were also included in regression models.

Analysis

Cause-specific Cox Proportional Hazards models were created using each major cause of death category as the outcome. Due to the presence of competing risks in this analysis, an alternative measure of risk was also used: the subdistribution cumulative incidence function (39). Other causes of death not associated with the cause of death category of interest were identified as competing risks for this study. The calculated functions were also used to create stacked cumulative incidence plots. The plots display how the total probability of one is allocated between all competing risks, including the possibility of surviving through the end of follow-up.

All models used follow-up time (time since interview) as the time axis. The hazards were determined to lack proportionality across the full 40 year follow-up time period based on the examination of Schoenfeld residuals and log-log plots. Follow-up time was stratified into three periods: 0–14.99 years, 15–29.99 years, and 30–40 years. The sample was stratified by sex and three main baseline age ranges: young adult (18–39 years), middle-aged (40–64), and elderly (≥65) according to hypotheses related to sex and age interactions. Sensitivity analyses were conducted by removing participants who died during the first 5 years of follow-up time from the at-risk population to exclude individuals who may have been physically ill at baseline. All analyses were performed in Stata v.11 (40).

Results

Table 1 displays the main characteristics and cause of death information for the population. The study population comprised the entire adult age span (18–95 years) with middle-aged adults (40–64 years) forming the largest age group (43.1%). The study population was almost exclusively white, Caucasian race (97.8%).

A total of 467 (16.9%) participants had depressed mood at baseline (CES-D score ≥16). Participants with depressed mood were mainly female and younger than participants without depressed mood. Prevalence of depressed mood decreased with age. Only 12.5% of elderly participants displayed elevated symptoms compared to 21.0% of young adults and 15.1% of middle-aged adults.

The majority of the cohort (56.0%, n=1546) was determined deceased by the end of follow-up. There were no statistically significant differences for major causes of death between participants with and without depressed mood. Cardiovascular disease and cancer were the leading causes of death for both populations. Few participants died from fatal injuries in either group. Twelve suicide deaths occurred in this study population and all were in male participants. Ten suicide deaths occurred among participants without elevated depressive symptoms at baseline.

Relative hazards for specific causes of death for all participants are shown in Table 2. The cardiovascular risk estimate (1.30 (1.05–1.60) – subdistribution hazard ratio) was statistically significant. Removal of deaths occurring in the first 5 years of follow-up time had no major impact on the risk estimate (1.36 (1.08–1.71)). The association between depressed mood and fatal injuries was pronounced during the first 15 years of follow-up (2.50 (1.03–6.02)) and then null afterwards. All associations with cancer deaths were consistently null.

Relative hazards for participants aged 18–39 years at baseline are displayed in Table 3. The relative hazards for cardiovascular deaths (3.08 (1.74–5.45)) and fatal injuries (4.63 (1.76–12.18) were significant over the entire 40-year period. Removal of deaths occurring in the first 5 years of follow-up strengthened the association with fatal injuries (5.22 (1.89–14.45)). The risk estimate for cardiovascular deaths did not change.

The association between depressed mood and fatal injuries was confined to the first 15 years of follow-up (8.65 (2.05–36.45)). The high risk of fatal injuries within the early follow-up time period was linked to deaths among males with depressed mood. Three deaths total occurred in this group; all were related to fatal injuries: motor vehicle accident, suicide, and homicide.

The association between depressed mood and elevated cardiovascular death risk was linked to deaths in females. Relative hazards could not be calculated for young adult females during the immediate follow-up time period since no cardiovascular deaths occurred in females without depressed mood; 4 cardiovascular deaths occurred in females with depressed mood out of 8 deaths total. During the last 10 years of follow-up, 50.0% of deaths among females with depressed mood were cardiovascular-related versus 13.6% of deaths in females without depressed mood. This resulted in a relative subdistribution relative hazard of 6.18 (1.39–27.46).

The differences between young adults with and without depressed mood can are further highlighted in Figures 1 and 2. Young adult males (Figure 1) with depressed mood displayed higher total mortality (36.2% vs. 18.8%, $P<.001$). The stacked cumulative incidence functions for the 4 main cause of death categories appeared similar between males with and without depressed mood. The reverse can be seen for females (Figure 2). Females with depressed mood did not display significantly higher total mortality (16.8% vs. 11.9%, $P=0.12$), but higher cumulative incidence functions for cardiovascular and injury mortality.

The most noticeable difference among middle-aged participants was the lack of fatal injuries among those with depressed mood. Only one fatal injury occurred among middle-aged participants with depressed mood. The death (a motor vehicle accident) occurred in a female. Twenty fatal injuries occurred in middle-aged males without depressed mood. Five of these deaths (25%) were due to suicide and seven (35%) were related to accidental falls. There were no sustained significant associations between cardiovascular or cancer deaths and depressed mood for middle-aged participants over the full 40-year follow-up period.

Significant findings for the elderly age group were limited to the 0–15 year follow-up period. Elevated estimates for both cardiovascular and injury deaths were calculated, but only cardiovascular remained statistically significant (1.75 (1.20–2.56)). As very few participants survived to the last stage of follow-up, reliable risk estimates could not be calculated. Associations with cancer deaths remained null.

The cardiovascular association was linked to males in this age group. During the first 15 years of follow-up, 91.7% of all deaths among males with depressed mood were cardiovascular related, resulting in an associated relative subdistribution hazard of 2.99 (1.67–5.37).

Discussion

Findings from this study involving a 40-year follow-up period, suggest persistent associations between depressed mood and cause-specific mortality that differ by sex, age group, and proximity to baseline. Even several decades after baseline, young adult females with depressed mood remained at excess risk of death from cardiovascular disease. Young

adult males with depressed mood were at excess risk of fatal injury in time periods closer to baseline.

Our findings confirm those from other community-based studies (28, 29, 41, 42): the total mortality associated with depression in the general community is driven by common causes of death. Individuals with depressed mood in this study died from the same diseases as individuals without depressed mood: mainly cardiovascular disorders and cancer. Our findings confirm previously reported findings that the excess mortality risk associated with depression is not explained by excess suicide deaths (28).

The majority of suicide deaths in this study occurred among individuals without depressed mood, a previously reported finding (31). Fatal injuries were important causes of death among middle-aged males without depressed mood. Fatal injuries were the only causes of death for young adult males with depressed mood during the first twenty years of follow-up. Other studies have indicated that deaths related to hazardous behaviors often occur before middle-age for many males experiencing depression (43–45). The middle-aged males with depressed mood in this study may have represented the lower end of the fatal injury risk spectrum; the highest end population may have been deceased by study entry.

The association between depression and excess risk of cardiovascular death has been a common finding of studies involving older adults (46–49). The current study allowed identification of another distinct group who experienced similar excess risk: young adult females. Young adult females with depressed mood may have experienced cardiovascular mortality on a completely different trajectory as the elderly males with depressed mood in this population. Emergence of depression in young adulthood is believed to have a strong genetic basis versus a direct link to pre-existing illness (50). The genetic link to depression may be associated with future development of cardiovascular disease (51, 52). Recent analyses of NHANES III have also suggested young adult females with depression may be at excess risk of premature cardiovascular related death over a 15-year follow-up period (53). Results from this current study augment these findings by indicating this excess risk may extend into late adulthood for females experiencing depression as young adults.

The null findings related to cancer deaths are consistent with many studies (11–13, 54). A prior study in this population (10) with more limited follow-up did indicate an association between depressed mood and respiratory-related cancers in the presence of smoking. The current analysis was not site-specific. Furthermore, depressed mood was only associated with smoking in the young adult population. Given that the average age of lung cancer death is 72 years (55), more follow-up time may be needed to fully evaluate whether depressed mood is associated with certain site-specific cancers.

Data are limited regarding the presence of pre-existing illnesses among study participants. Data were collected on whether individuals dying very early in follow-up (e.g. <5 years) were ill at the time of interview. Individuals with depressed mood were less likely to have evidence of prior illness. Whether individuals dying in later time periods were physically ill at baseline remains unknown. The young adult females with depressed mood who died 30–40 years after baseline most likely did not have active, cardiovascular disease at baseline.

The accuracy of death certificate information has been questioned for decades. Studies have indicated the overrepresentation of circulatory disorders (56) and the blurred line between intentional and unintentional injuries (57). The use of a broader injury category better captured misclassification between unintentional and intentional injury. Studies also suggest that misclassification along a spectrum of disease like cardiovascular disease is more common than misclassification between separate major disease categories (56).

Depression is now considered to be the leading cause of disability in the world (58). Understanding of how depression contributes to mortality is obscured though. General community studies should continue exploring total mortality risk with consideration how cause-specific risks may differ. Depression is a serious, common illness often emerging early in adulthood. The expectation that depression has a wide influence on mortality should be agreed upon today.

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Abbreviations and acronyms

CES-D	Center for Epidemiologic Studies Depression scale
CI	Confidence interval
CMHE	Community Mental Health Epidemiology Program study
ICD	International Classification of Disease
NDI	National Death Index
SSDI	Social Security Death Index

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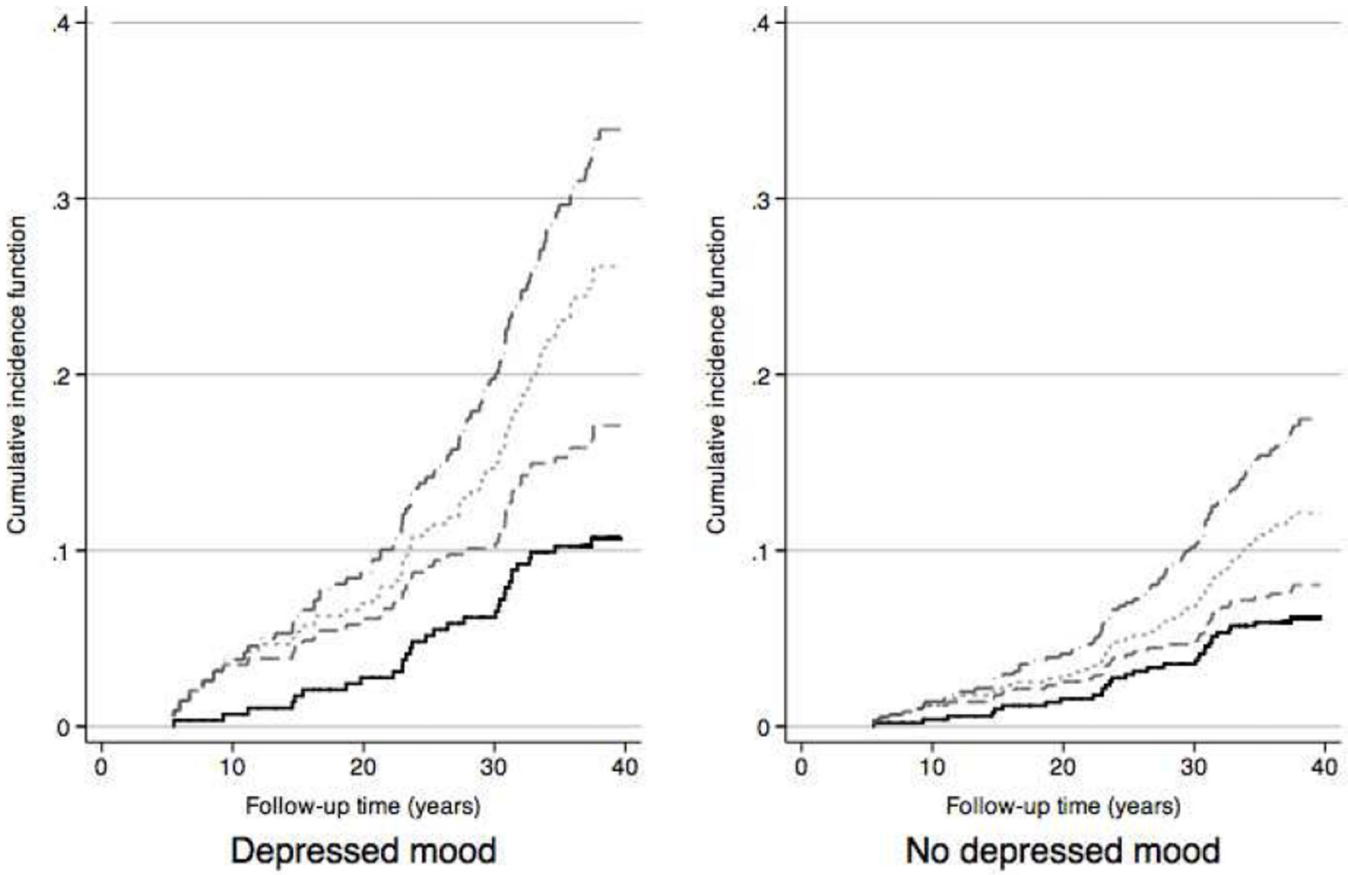

Figure 1.
Stacked cumulative incidence plots for specific causes of death, males 18–39 years old at baseline

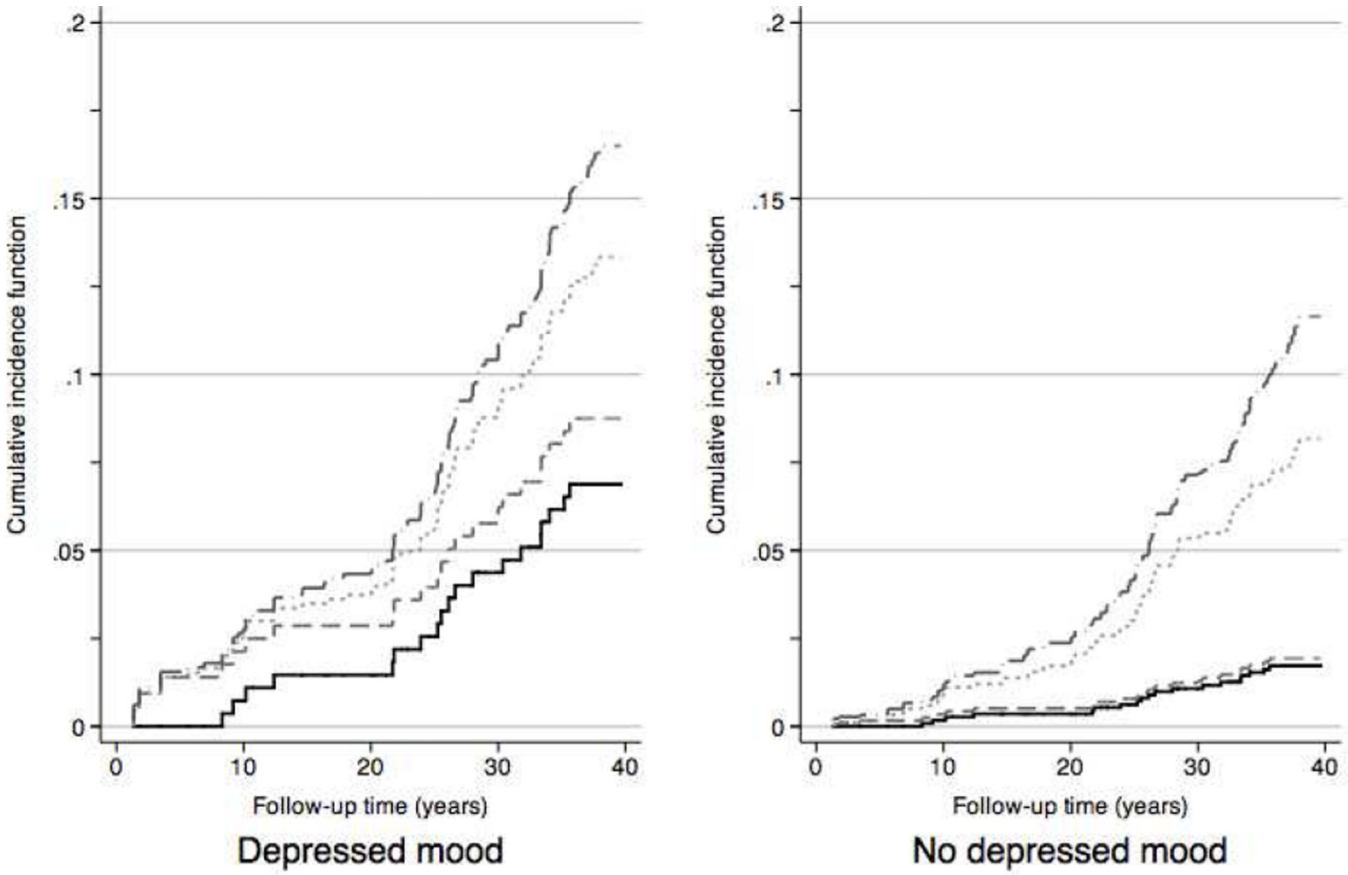

Figure 2.
Stacked cumulative incidence plots for specific causes of death, females 18–39 years old at baseline

Table 1

Baseline characteristics and main causes of death for all participants, stratified by baseline depressed mood status

Variable	Category	Total 2,762		Depressed mood[1] n=467 (16.9%)		No depressed mood n=2,279 (82.5%)		Comparison: *P* value
		n	%	n	%	n	%	
Age	Mean (SD)	46.69 (17.37)		42.56 (17.38)		47.45 (17.25)		<.001
Age group	18–39	1,101	39.9	231	49.5	869	38.1	<.001
	40–64	1,190	43.1	178	38.1	1,003	44.0	
	≥ 65	471	17.1	58	12.4	407	17.9	
Sex	Female	1,607	58.3	329	70.5	1,267	55.6	<.001
	Male	1,154	41.8	137	29.3	1,012	44.4	
Deaths	All cause	1547	56.0	244	52.3	1290	56.6	.08
	Cardiovascular[2]	726	26.3	112	24.0	355	26.7	.23
	Cancer[3]	327	11.8	50	10.7	273	12.0	.44
	Injury[4]	56	2.0	10	2.1	45	2.0	.82
	All other causes	438	15.9	72	15.4	364	16.0	.77

[1] Depressed mood measured as Center for Epidemiologic Studies Depression scale (CES-D) score ≥16; CES-D score missing for 16 (.58%) participants

[2] Cardiovascular= Diseases of the heart, cerebrovascular diseases, essential hypertensive renal disease

[3] Cancer= Any malignant neoplasm

[4] Injury= Unintentional injuries, suicides, and homicides

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Table 2

Hazard ratios for the association between depressed mood and cause-specific mortality, stratified by cause of death and follow-up time period in years for all participants

Follow-up time	Cause of death	Number of deaths (% of all-cause deaths)			Subdistribution hazard ratio: Age/sex adjustment[4]		Cause-specific hazard ratio: Age/sex adjustment[4]	
		Total	Depressed mood	No depressed mood	Point estimate	95% CI	Point estimate	95% CI
0–15	CVD[1]	333(56.5)	51(52.6)	282(58.1)	1.54	1.15–2.00	1.56	1.15–2.11
	Injury[2]	24(4.1)	7(7.2)	17(3.5)	2.50	1.03–6.02	2.67	1.08–6.58
	Cancer[3]	124(21.1)	16(16.5)	108(22.3)	1.18	.69–1.79	1.08	.63–1.84
15–30	CVD	285(43.7)	45(45.9)	240(43.8)	1.37	.99–1.91	1.40	1.01–1.94
	Injury	23(3.5)	2(2.0)	21(3.8)	.78	.19–3.16	.80	.18–3.47
	Cancer	142(21.8)	22(22.4)	120(21.9)	1.11	.69–1.79	1.17	.74–1.85
30–40	CVD	101(33.1)	16(32.7)	85(33.2)	1.22	.71–2.09	1.34	.77–2.31
	Injury	8(2.6)	1(2.0)	7(2.7)	1.44	.23–8.87	.87	.11–7.29
	Cancer	57(18.7)	12(24.5)	45(12.6)	1.10	.34–3.57	1.64	.85–3.15
All years	CVD	720(46.6)	112(45.9)	608(47.2)	1.30	1.05–1.60	1.46	1.19–1.80
	Injury	55(3.6)	10(4.1)	45(3.5)	1.34	.68–2.63	1.55	.77–3.11
	Cancer	323(20.9)	50(20.5)	273(21.2)	.79	.39–1.58	1.22	.90–1.66

[1]Cardiovascular= Diseases of the heart, cerebrovascular diseases, essential hypertensive renal disease

[2]I Injury= Unintentional injuries, suicides, and homicides

[3]Cancer= Any malignant neoplasm

[4]Full adjustment (age, sex, smoking, education, and body weight) did not alter significant findings

Table 3

Hazard ratios for the association between depressed mood and cause-specific mortality, stratified by cause of death and follow-up time period in years for participants 18–39 years

Follow-up time	Cause of death	Number of deaths (% of all-cause deaths)			Subdistribution hazard ratio: Age/sex adjustment[4]		Cause-specific hazard ratio: Age/sex adjustment[4]	
		Total	Depressed mood	No depressed mood	Point estimate	95% CI	Point estimate	95% CI
0–15	CVD[1]	8(26.1)	4(36.4)	4(21.1)	5.38	1.66–17.47	5.60	1.37–22.86
	Injury[2]	8(26.7)	5(45.5)	3(15.8)	8.65	2.05–36.45	8.66	2.01–37.43
	Cancer[3]	6(20.0)	2(18.2)	4(21.1)	2.02	.36–11.26	2.07	.37–11.71
15–30	CVD	22(29.7)	7(36.8)	15(27.3)	2.53	1.05–6.11	2.53	1.02–6.28
	Injury	2(2.7)	1(5.3)	1(1.8)	Not calculated[5]		Not calculated[5]	
	Cancer	29(39.2)	7(36.8)	22(40.0)	1.46	.59–3.60	1.46	.62–3.45
30–40	CVD	20(25.3)	7(31.8)	13(22.8)	3.28	1.79–8.35	3.37	1.32–8.59
	Injury	5(6.3)	1(4.5)	4(7.6)	1.44	.23–8.87	1.54	.17–14.37
	Cancer	22(27.8)	4(18.2)	18(31.6)	1.10	.34–3.57	1.17	.39–3.52
All years	CVD	50(27.3)	18(34.6)	32(24.4)	3.08	1.74–5.45	3.26	1.81–5.86
	Injury	15(8.2)	7(13.5)	8(6.1)	4.63	1.76–12.18	4.80	1.70–13.57
	Cancer	57(31.1)	13(25.0)	44(33.6)	1.30	.67–2.53	1.41	.75–2.64

[1]Cardiovascular= Diseases of the heart, cerebrovascular diseases, essential hypertensive renal disease

[2]Injury= Unintentional injuries, suicides, and homicides

[3]Cancer= Any malignant neoplasm

[4]Full adjustment (age, sex, smoking, education, and body weight) did not alter significant findings

[5]Estimates not calculated due to insufficient number of deaths