Depressive Symptoms and All-Cause Mortality in a Nationally Representative Longitudinal Study With Time-Varying Covariates

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Objective: To examine the relationship between depressive symptoms and all-cause mortality in a longitudinal study with a nationally representative sample. Research has shown that depressive symptoms increase mortality risk, but results have been inconclusive regarding the role of physical health conditions in the relationship. This study asks whether the association between depressive symptoms and mortality exists independent of *contemporaneous* physical health conditions, is spurious because of *prior* physical health conditions, or is mediated by *later* physical health conditions. **Methods:** Data are drawn from the Americans' Changing Lives Study, a sample of 3617 noninstitutionalized Americans aged 25 years or older. Respondents were interviewed in 1986, 1989, 1994, and 2002. Depressive symptoms (Center for Epidemiologic Studies Depression Scale [CES-D]), physical health, and confounders were measured at each wave. Mortality status was ascertained yearly through 2007. Discrete time hazard models with time-varying covariates were used to estimate the association between CES-D scores and mortality. **Results:** Between 1986 and 2007, 1411 survey respondents died. Depressive symptoms were associated with mortality after adjusting for stress, coping characteristics, social support, and health behaviors (odds ratio [OR] = 1.23, 95% confidence interval [CI] = 1.11–1.36, $p < .001$). However, the association became nonsignificant after accounting for contemporaneous physical health conditions (OR = 1.06, 95% CI = 0.95–1.17, $p = .31$). Prior physical health conditions did not explain the association (OR = 1.24, 95% CI = 1.11–1.39, $p < .001$). The association between lagged depressive symptoms and mortality was mediated by later physical health conditions ($p = .94$). **Conclusions:** Study findings support the mediation hypothesis. The effect of depressive symptoms on mortality is mediated by later physical health. **Key Words:** depressive symptoms, mortality, time-varying covariates, Americans' Changing Lives Survey.

CES-D = Center for Epidemiologic Studies Depression Scale; **ACLS** = Americans' Changing Lives Study; **CVD** = cardiovascular and/or cerebrovascular disease.

INTRODUCTION

Numerous studies have shown that depression and depressive symptoms are associated with an increased risk of all-cause mortality (1–4). This association has been shown across a variety of community studies (1,3) and nationally representative samples (5–7). This association persists across a wide range of causes of death and is not limited to suicide or cardiovascular disease (CVD) mortality (8). Questions remain, however, about whether the relationship is spurious or causal, and if it is causal, what are the mechanisms that explain the association? Physical health conditions are thought to play a role (5), but it is not clear whether the association persists net of contemporaneous physical health, is mediated by contemporaneous physical health, or is rendered spurious by preexisting physical health conditions (1,3,6).

One hypothesis is that depression is an independent risk factor for mortality, much like smoking, hypertension, or stroke (9). For example, Schulz and colleagues (3) find that baseline depression is associated with mortality 6 years later, after adjusting for baseline smoking, alcohol use, and physical illness. This study concludes that "motivational depletion," rather than physical illness, is the main mechanism that links depression and mortality (3). This hypothesis, which I term the *Independent Hypothesis*, predicts that the association between depression and mortality persists net of *contemporaneous* confounders, including physical health conditions.

A second hypothesis is that the association between depression and mortality is spurious and that exogenous third factors—such as physical health—influence both depressive symptoms and mortality. For example, it is well known that physical health conditions (such as chronic conditions and functional impairment) and health behaviors increase the risk for both depression and mortality. (3,4,10,11). Other previously unmeasured confounders such as exposure to stress, coping resources, and social support may also render the association spurious (12–15). This hypothesis, the *Spurious Hypothesis*, predicts that prior (lagged) physical health conditions and other confounders increase the risk for later depression and mortality. That is, preexisting physical health conditions, health behaviors, and other confounders fully explain the relationship between depressive symptoms and mortality.

A third hypothesis is that depression is a risk factor for mortality, but that this relationship is mediated by physical health conditions and health behaviors (4,5,16). Unlike the spurious hypothesis, which predicts that physical health renders the association between depression and mortality spurious, the *Mediation Hypothesis* predicts that *later* physical health conditions are a primary mechanism linking depression to mortality. That is, the association between depressive symptoms and mortality is fully mediated by later physical health conditions.

Prior research has been unable to adjudicate between these three hypotheses because it has relied on research designs that measure depression and confounders at one point in time with a mortality follow-up several years later. For example, Everson-Rose and colleagues (5) find that the association between baseline depressive symptoms and mortality is explained by baseline physical health conditions. However, because

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depression, physical health, and other confounders are measured only at baseline, it is not clear whether this finding supports the spurious hypothesis or the mediation hypothesis.

The focus of the present study is to overcome the limitations of prior research and provide a test of the three hypotheses described above (Fig. 1). To achieve this end, this study uses a nationally representative longitudinal sample with repeated measures of depressive symptoms, confounders, and mediators at four time points: 1986, 1989, 1994, and 2002. Mortality status is assessed annually through 2007. This data structure allows depressive symptoms, physical health, and confounders to vary over time. This study therefore builds on prior research that measures depressive symptoms and confounders at a single point in time and takes a step toward understanding how the link between depressive symptoms, physical health, and mortality unfolds over time.

DATA AND METHODS

Data

This study uses data from the Americans' Changing Lives Survey (ACLS). The ACLS is a multistage stratified area probability sample of noninstitutionalized persons older than 25 years in 1986 who resided in the continental United States (17). It also oversamples African Americans and persons 60 years and older. The sampling strategy ensures that the survey is nationally representative of noninstitutionalized adults 25 years or older in 1986. Respondents were first interviewed in 1986 with an 80-minute face-to-face interview (n = 3617; response rate, 70%) and were followed up in 1989 (n = 2867), 1994 (n = 2562), and 2002 (n = 1786). For more information on the ACLS, see House and colleagues (18).

Missing data were handled using listwise deletion. All results are weighted and corrected for sample design. All independent variables in the study (including depression, physical health, health behaviors, and confounders) were measured at all survey waves, with the exception of sex, race, educational attainment, and extraversion (Wave 1 only). See Table 1 for descriptive statistics for all variables included in the study.

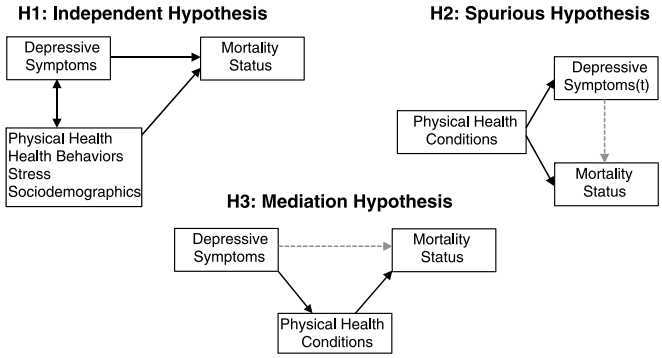

Figure 1. Three hypotheses of the relationship between depressive symptoms and all-cause mortality. Note: the gray-scaled dotted arrows signify a significant association that is explained to nonsignificance by the confounding (H2) or mediating (H3) variables.

TABLE 1. Respondent Characteristics at Baseline (1986), Americans' Changing Lives Survey

	Mean	Range	%
Depressive symptoms (CES-D score)	0.0	−1.2 to 4.5	
Mortality status (through 2007)			
Alive			74.0
Dead			26.0
Age, y	47.1	24–96	
Sociodemographics			
Sex			
Women			52.9
Men			47.1
Race			
Black			10.7
Nonblack			89.3
Family income (bracketed)	5.3	1–10	
Educational attainment (bracketed)	3.3	1–6	
Marital status			
Never married			0.1
Divorced/Separated			0.1
Widowed			0.1
Married			0.7
Employment status			
Unemployed			0.0
Employed			1.0
Stress, coping, and social support			
Chronic financial stress	0.0	−1.8 to 2.7	
Chronic parenting stress	0.0	−1.6 to 4.7	
Chronic marital stress	1.8	0–7	
Recent stressful life events	0.9	0–6	
Mastery	0.0	−3.1 to 1.3	
Extraversion (personality)	0.0	−1.7 to 1.3	
Formal social integration index	0.0	−1.6 to 2.0	
Informal social integration index	0.0	−3.1 to 1.4	
Health behaviors			
BMI			
Underweight			5.1
Normal weight			79.6
Overweight			15.3
Smoking status			
Nonsmoker			69.6
Smoker			30.4
Alcohol use			
Abstain			41.2
Moderate drinker			54.5
Heavy drinker			4.3
Physical activity index			
Low activity			26.2
Moderate activity			34.9
High activity			38.9
Physical health conditions			
No. debilitating chronic conditions	0.6	0–4	
No. life-threatening chronic conditions	0.2	0–3	
Recent serious illness or injury			19.5
Health limitations	0.6	0–4	
Functional impairment index	0.3	0–3	

CES-D = Center for Epidemiologic Studies Depression Scale; BMI = body mass index.

All descriptive statistics were adjusted for sample design. n = 3617; 1411 deaths.

Measures

Mortality

Year of death was ascertained by ACLS staff members via the National Death Index or proxy report and was verified with obituaries. Mortality data have been collected since, directly after the first wave of data collection (1986) until 2007. Cause of death is assessed using the *International Statistical Classification of Disease, Tenth Edition*. A total of 1411 of the original 3617 respondents died by 2007 (39%). After accounting for sample design with weights, 26% of the sample had died by 2007. Further analysis revealed that average age at death and age-specific death rates in this sample are largely equivalent to national estimates.

Depressive Symptoms

Depressive symptoms were measured using an 11-item version of the Center for Epidemiologic Studies Depression Scale (CES-D) (19). At each survey wave, respondents were asked to what extent they felt depressed, that everything was an effort, sleep was restless, was happy (reverse coded, felt lonely, people were unfriendly, enjoyed life (reverse coded), did not feel like eating, felt sat, people disliked me, and could not get going in the past week. Responses ranged from 1 (hardly ever) to 3 (most of the time). Responses were summed, and the final scale was normalized with a mean of 0 and standard deviation (SD) of 1.

Physical Health Conditions and Health Behaviors

Physical health conditions include the number of debilitating chronic health conditions, the number of life-threatening health conditions, functional impairment index, health limitations, and serious illness or injuries at each survey wave. Number of debilitating chronic health conditions is a summation of reports of hypertension, broken bones, arthritis or rheumatism, and bladder control problems in the past year. Number of life-threatening chronic conditions is a summation of reports of diabetes, lung diseases, myocardial infarction or heart disease, stroke, or cancer in the past year. Functional impairment is constructed from a series of questions that ask respondents the extent to which they are forced to sit in a chair or bed all day, have difficulty or need assistance bathing, have difficulty climbing stairs, have difficulty walking blocks, and have difficulty with heavy work around the house. The Functional Impairment Index is a Gutman scale coded from highest or most severe functional impairment (4) to the lowest (1). Health limitations are a measure of the extent to which respondents feel their physical health limits their daily activities. Responses range from a great deal (1) to not at all (5). The study also adjusts for whether or not respondents experienced a life-threatening or serious injury/illness in the past 3 years (1 = yes).

Health behaviors at each survey wave are operationalized with smoking status (1 = smoker; 0 = nonsmoker), alcohol use (abstainer; moderate use, 1–89 drinks/mo; heavy use, 90+ drinks/mo), body mass index (underweight, normal weight [reference], overweight) and a physical activity index. Physical activity is an index constructed from mean responses to three physical activity items: how often the respondent reports working in the garden or yard (1 = always; 4 = never), take walks, or engage in sports or athletics. The physical activity index is standardized with a mean of 0 and an SD of 1 and recoded into tertiles to reflect low, moderate, and high physical activity.

Sociodemographic Characteristics

Sociodemographic characteristics include sex (female = 1; male = 0), race (1 = nonwhite, 0 = white), employment status (1 = unemployed, 0 = employed), marital status (never married, divorced/separated, married [reference], or widowed), age (in years), respondent's level of education, and family income. Family income is coded in deciles. Missing data on income were multiply imputed by ACLS staff (20). Education is a six-category ordinal variable bracketed by years, where 1 indicates 0 to 8 years of education; 2, 9 to 11 years; 3, 12 years (high school degree); 4, 13 to 15 years; 5, 16 years (college degree); and 6, 17 years or more.

Life Stress, Social Support, and Personal Coping Resources

Measures of life stress, social support, and personal coping resources were selected to reflect measures commonly used in stress process research (21). Life stress is operationalized using four measures of stress (15)—the number of stressful life events reported by the respondent since the last survey wave, chronic financial stress, chronic marital stress, and chronic parenting stress. The number of stressful life events is a summation of whether or not respondents experienced divorce, death of a spouse, death of a child, physical attack or assault, death of a parent, death of a friend, involuntary job loss, robbery or burglary, and other events that caused them to be upset. Chronic financial stress is a scale constructed from the average response to questions where respondents were asked how satisfied they are with their family's financial situation, how difficult it is to make ends meet, and if enough money is leftover after paying bills each month. It is standardized with a mean of 0 and an SD of 1. Chronic parenting stress is a scale constructed from the average response to questions where respondents were asked how satisfied they are with being a parent, how often they feel bothered or upset as a parent, and how happy they are with how their child/ren turned out to this point. It is standardized with a mean of 0 and an SD of 1. Following Lantz and colleagues (15), respondents without children are assigned the lowest value on the scale (instead of missing), and a dummy variable indicating parental status is included in the multivariate models. Chronic marital stress is a scale constructed from the average response to questions where respondents who were married or lived with a romantic partner were asked whether they agree with the statement "my spouse/partner doesn't treat me as well as I deserve"; "I sometimes think of divorcing or separating from my spouse/partner"; "There are things in my marriage/relationship that I can never forgive"; and how often the respondent has unpleasant disagreement with their spouse/partner. It is standardized with a mean of 0 and an SD of 1. Like the measure of chronic parental stress,

nonpartnered respondents are assigned the lowest value on the scale, and a dummy variable indicating partnership status is included in the multivariate analysis.

Social support is operationalized using two scales indicating informal and formal social integration. Informal social integration is operationalized from the mean response from questions where respondents were asked how often they talked on the telephone and spent time with friends and family. Responses ranged from more than once a week (1) to never (6). Formal social integration is operationalized from the mean response from questions where respondents were asked how often they attended meetings of any clubs or organizations to which they belonged, including religious services. Both scales were standardized with a mean of 0 and an SD of 1 and were recoded, so higher scores indicate higher levels of social integration.

Measures of coping resources include a two-item version of the Pearlin Mastery scale (22) and one of the Big Five Personality traits—extraversion (23,24). Extraversion is a stable personality trait that indicates the extent to which individuals are outgoing, gregarious, and talkative. The above scales or indexes were standardized with a mean of 0 and an SD of 1. Both Mastery (the extent to feel one has control over their lives) (22) and Extraversion (25,26) are established measures of coping resources in the stress literature.

Analysis Strategy

This study uses discrete time event history models to analyze the association between depressive symptoms and mortality over a 21-year period. Although most research on this topic uses continuous time Cox hazard regression models, more than 50% of events (deaths) in the data are ties (meaning they occur in the same year). Because continuous time models are not suited to deal with such a large number of ties, I instead use discrete time event history models (27). Data are converted into a person-period (or person-year) data set using the "psrnprd" command in STATA 12.0. In this person-year data set, depression, health, and confounders are allowed to vary over the years of observation. After accounting for left truncation, the final sample size is 47,861 person-years.

The analysis includes three types of variables. *Time-invariant variables* are measured at only one point in time. The only time-invariant variables in the study are sex, race, educational attainment, and extraversion. *Time-varying variables* are variables that are allowed to vary over time, across waves of study. These variables are measured at Waves 2, 3, and 4. Time-varying variables are denoted with the script (t) in tables and text. *Lagged time-varying variables* are variables that are coded to reflect the value of the variable at the prior wave of study. Lagged variables are measured at Waves 1, 2, and 3. Lagged variables are denoted with the script ($t - 1$) in tables and text.

RESULTS

Table 2 shows results from models testing the first study hypothesis (independent hypothesis)—whether the association between depressive symptoms (t) and mortality is fully explained by contemporaneous physical health conditions (t) and confounders (t). The variables in these models are all time varying (t), with the exception of sex, race, educational attainment, and extraversion, which are measured at Wave 1 only. Model 1 shows that after adjusting for sociodemographic characteristics, a 1-standard unit increase in depressive symptoms (t) is associated with a 28% increase in mortality risk (odds ratio [OR] = 1.28, $p < .001$). The association increases slightly after adjusting for stress process variables in Model 2 (OR = 1.30, $p < .001$). Model 3 shows that depressive symptoms remain significantly associated with mortality after adjusting for contemporaneous body mass index, smoking, alcohol use, and physical activity, although the effect is attenuated slightly. The association between depressive symptoms and mortality is reduced to nonsignificance after adjusting for chronic health conditions, health limitations, and functional impairment (OR = 1.06, $p = .31$). Supplementary analyses reveal that adjusting for functional impairment and health limitations explains the largest proportion of the association between depressive symptoms and mortality. Finally, stressful life events seem to have a protective effect on mortality, although the association is small and does not substantially alter the association between depression and mortality.

Table 3 shows results from models testing the spurious hypothesis. These models assess whether the effect of depressive symptoms on mortality is rendered spurious by prior (lagged) physical health conditions and test the effect of depressive symptoms (t) on mortality, net of lagged health conditions ($t - 1$). Model 1 includes depressive symptoms (t), sociodemographics (t), and health behaviors (t). Model 2 adds lagged measures of physical health conditions ($t - 1$). Because we know little about depression before survey observation and because prior depression influences current depression and health, these models also include a lagged ($t - 1$) measure of depressive symptoms. Thus, these models test whether *net* of one's previous health, depression status and other confounders, and depression influences risk of mortality at follow-up. Model 1 shows that a 1-standard unit increase in depressive symptoms (t) is associated with a 25% increase in mortality risk (OR = 1.25, $p < .001$). Model 2 shows that after accounting for lagged ($t - 1$) physical health conditions, this association is attenuated only slightly and remains statistically significant (OR = 1.24, $p < .001$).

Table 4 shows results from models testing the third study hypothesis (mediation hypothesis).These models assess whether the effect of depression on mortality is mediated by later physical health conditions and assess whether the effect of lagged depressive symptoms ($t - 1$) on mortality is explained by later physical health conditions (t). Model 1 includes lagged depressive symptoms ($t - 1$), sociodemographics ($t - 1$), and health behaviors ($t - 1$), and time-invariant variables (sex, race, education, extraversion). Model 2 adds time-varying physical health conditions (t). Model 1 shows that a 1-standard unit increase in lagged depressive symptoms ($t - 1$) is associated with a 13% increase in mortality risk at follow-up (OR = 1.13, $p = .02$). Note that the effect of depressive symptoms is smaller than previous models. This is because lagged ($t - 1$) measures

TABLE 2. Depressive Symptoms and All-Cause Mortality (*t*), Adjusting for Time-Varying Covariates (*t*) in the Americans' Changing Lives Study, 1986 to 2007

	Model 1[a]			Model 2[a]			Model 3[a]			Model 4[a]		
Variable	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
CES-D score[b]	1.28	1.17–1.39	<.001	1.30	1.17–1.43	<.001	1.23	1.11–1.36	<.001	1.06	0.95–1.17	.31
Chronic financial stress				1.05	0.94–1.16	.40	1.04	0.93–1.15	.67	0.99	0.89–1.11	.87
Chronic marital stress				0.88	0.75–1.03	.13	0.90	0.77–1.05	.19	0.90	0.78–1.05	.19
Chronic parenting stress				0.97	0.87–1.08	.57	0.97	0.87–1.08	.53	0.98	0.88–1.08	.64
Recent stressful life events				0.87	0.79–0.96	.020	0.88	0.80–0.97	.012	0.86	0.77–0.95	.003
Mastery				0.96	0.88–1.05	.37	0.97	0.88–1.07	.53	0.97	0.88–1.06	.54
Extraversion (time invariant)				1.00	0.91–1.10	.91	1.00	0.90–1.10	.92	0.97	0.88–1.06	.52
Formal social integration				0.88	0.80–0.96	.003	0.93	0.86–1.02	.13	0.95	0.87–1.03	.24
Informal social integration				0.96	0.88–0.11	.38	0.98	0.89–1.07	.66	0.98	0.89–1.07	.65
BMI												
Underweight							2.48	1.85–3.32	<.001	2.26	1.69–3.02	<.001
Normal weight								Referent			Referent	
Overweight							0.93	0.74–1.16	.53	0.86	0.68–1.08	.19
Smoking status												
Nonsmoker								Referent			Referent	
Smoker							1.71	1.30–2.24	<.001	1.82	1.38–2.39	<.001
Alcohol use												
Abstain								Referent			Referent	
Moderate drinker							0.77	0.63–0.94	.010	0.87	0.71–1.07	.20
Heavy drinker							0.65	0.30–1.42	.28	0.86	0.39–1.85	.69
Physical activity												
Low								Referent			Referent	
Moderate							0.60	0.48–0.75	<.001	0.74	0.59–0.93	.010
High							0.68	0.53–0.87	.002	0.90	0.69–1.17	.44
No. chronic conditions												
Debilitating conditions										0.95	0.85–1.07	.41
Life-threatening conditions										1.37	1.21–1.55	<.001
Recent serious illness or injury										1.34	1.10–1.63	.003
Health limitations										1.11	1.03–1.21	.010
Functional impairment index										1.27	1.14–1.41	<.001
Constant	0.00	0.00–0.00	<.001	0.00	0.00–0.00	<.001	0.00	0.00–0.01	<.001	0.00	0.00–0.01	<.001
Pseudo-R^2	0.17			0.18			0.19			0.21		

OR = odds ratio; CI = confidence interval; CES-D = Center for Epidemiologic Studies Depression Scale; BMI = body mass index.

Results are from discrete time event history models with time-varying covariates estimating the association between CES-D scores and all-cause mortality (2-tailed significance test). CES-D score is standardized with a mean of 0 and a standard deviation of 1. All analyses were adjusted for sample design, and all variables are time varying (*t*), unless otherwise noted. n = 47,861 person-years; 1411 deaths.

[a] Models also adjust for the following time-invariant and time-varying covariates: *time invariant*: sex, race, and educational attainment; *time varying:* age, age^2, family income, marital status, and employment status.

[b] The OR reflects the mortality risk associated with a 1-standard unit increase in the CES-D -score.

tend to have smaller associations with outcomes than current (*t*) measures. Model 2 shows that adjusting for later physical health conditions (*t*) reduces the association between lagged depressive symptoms ($t - 1$) and mortality to nonsignificance (OR = 1.00, p = .94). Supplementary models (see "Appendix 1") reveal that functional limitations and health limitations have the largest mediating effects.

Several additional models were estimated as a robustness check. First, following prior research that finds sex differences (6,28), I estimated models to test whether the association between depressive symptoms and mortality differs for men and women. It did not (depression * sex interaction term in Model 1: OR = 0.980, p = .81). Second, CES-D scores were recoded into quintiles: low depressive symptoms (25th percentile or below [reference]), mid-level depressive symptoms (26th–75th percentile), mid-high depressive symptoms (75th–89th percentile), high depressive symptoms (90–95th percentile), and highest depressive symptoms (95th percentile and above). Respondents with the highest depressive symptoms had the highest mortality risk before adjusting for

TABLE 3. Depressive Symptoms (*t*) and All-Cause Mortality, Adjusting for Lagged Physical Health Conditions (*t* − 1) in the ACLS, 1986 to 2007

Variable	Model 1[a]			Model 2[a]		
	OR	95% CI	*p*	OR	95% CI	*p*
CES-D score (t)[b]	1.25	1.12–1.40	<.001	1.24	1.11–1.39	<.001
Lagged physical health conditions (*t* − 1)						
No. chronic health conditions						
Debilitating conditions				1.07	0.95–1.20	.25
Life-threatening conditions				1.52	1.32–1.75	<.001
Recent serious illness or injury				1.00	0.81–1.22	.98
Health limitations				0.98	0.93–1.04	.52
Functional impairment index				1.15	1.05–1.27	.004
Constant	0.00	0.00–0.00	<.001	0.00	0.00–0.00	<.001
Pseudo-R^2	0.19			0.20		

ACLS = Americans' Changing Lives Study; OR = odds ratio; CI = confidence interval; CES-D = Center for Epidemiologic Studies Depression Scale.
Results are from discrete time event history models with time-varying covariates estimating the association between CES-D scores and all-cause mortality (2-tailed significance test). CES-D score is standardized with a mean of 0 and standard deviation of 1. All analyses were adjusted for sample design. n = 47,861 person-years; 1411 deaths.
[a] Models also adjust for the following time invariant and time-varying covariates: *time invariant*: sex, race, and educational attainment, and extraversion; *time varying:* age, age^2, family income, marital status, employment status, chronic financial stress, chronic parenting stress, chronic marital stress, stressful life events, mastery, formal and informal social integration, body mass index, smoking status, alcohol use, physical activity, and lagged depressive symptoms.
[b] The OR reflects the mortality risk associated with a 1-standard unit increase in the CES-D score.

physical health conditions. However, even respondents with mid-high levels of depressive symptoms had a significantly higher mortality risk than did respondents with low/no depressive symptoms. Models with the categorical CES-D measure revealed substantively and statistically equivalent results to models with the continuous CES-D measure. In addition, to ensure that the association between depression and mortality was not driven by the oldest old—and to ensure that the proportionality assumption was met (27)—I estimated additional models to test whether the association varied by age. It did not (age * CES-D: OR = 1.01, p = .55; age^2 * CES-D: OR = 0.99, p = .40).

Finally, to test whether the effect of depression on mortality differed by cause of death, I reestimated the above models for (1) CVD mortality and (2) all other causes of death (see online supplement for CVD tables, http://links.lww.com/PSYMED/A69).

TABLE 4. Lagged Depressive Symptoms (*t* − 1) and All-Cause Mortality, Adjusting for Physical Health Conditions (*t*) in the ACLS, 1986 to 2007

Variable	Model 1[a]			Model 2[a]		
	OR	95% CI	*p*	OR	95% CI	*p*
Lagged CES-D score (*t* − 1)[b]	1.13	1.02–1.26	.02	1.00	0.89–1.12	.94
Physical health conditions (*t*)						
No. chronic conditions						
Debilitating Conditions				0.96	0.86–1.07	.45
Life-threatening conditions				1.36	1.21–1.54	<.001
Recent serious illness or injury				1.34	1.10–1.62	.004
Health limitations				1.14	1.05–1.24	.001
Functional impairment index				1.28	1.16–1.43	<.001
Constant	0.00	0.00–0.00	<.001	0.00	0.00–0.00	<.001
Pseudo-R^2	0.19			0.21		

ACLS = Americans' Changing Lives Study; OR = odds ratio; CI = confidence interval; CES-D = Center for Epidemiologic Studies Depression Scale.
Results are from discrete time event history models with time-varying covariates estimating the association between CES-D scores and all-cause mortality (2-tailed significance test). CES-D score is standardized with a mean of 0 and standard deviation of 1. All analyses were adjusted for sample design. n = 47,861 person-years; 1411 deaths.
[a] Models also adjust for the following time-invariant and time-varying covariates: *time invariant*: sex, race, educational attainment, neuroticism, and extraversion personality traits; *time varying*: age, age^2, family income, marital status, employment status, chronic financial stress, chronic parenting stress, chronic marital stress, stressful life events, mastery, formal and informal social integration, body mass index, smoking status, alcohol use, physical activity, and lagged depressive symptoms.
[b] OR reflects the mortality risk associated with a 1-standard unit increase in the CES-D score.

The results for CVD mortality and other mortality were substantively and statistically equivalent to models predicting all-cause mortality. In results analogous to those shown in Table 2, there was a significant association between CES-D and mortality after accounting for health behaviors and stress process variables (CVD mortality: OR = 1.27, $p < .001$; other mortality: OR = 1.22, $p < .01$), which was fully explained by contemporaneous physical health conditions (CVD mortality: OR = 1.08, $p = .27$; other mortality: OR = 1.06, $p = .42$). Prior (lagged) physical health conditions did not explain the association between depressive symptoms and mortality (CVD mortality: OR = 1.33, $p < .001$; other mortality: OR = 1.25, $p = .007$). Instead, the association between depressive symptoms and mortality was mediated by later physical health conditions (CVD mortality: OR = 1.02, $p = .82$; other mortality: OR = 0.97, $p = .74$).

DISCUSSION

This study tests three hypotheses regarding the association between depressive symptoms and all-cause mortality. The "independent" hypothesis predicts that depression is an independent risk factor for mortality, net of health behaviors, physical health, stress, and other confounders. The "spurious" hypothesis predicts that the association is spurious and explained by prior physical health conditions. The "mediation" hypothesis predicts that physical health mediates the relationship between depression and mortality. The study finds support for the mediation hypothesis and shows no support for the independent or spurious hypotheses. Results show that physical health conditions and their changes over time mediate the relationship between depressive symptoms and mortality. In other words, the findings suggest that people who feel depressed are more likely to develop health problems (particularly functional limitations such as mobility problems and difficulty with daily activities) and, in turn, have a higher mortality risk compared with people who are not depressed. Such findings are consistent with prior research that shows that depression increases the risk for developing physical health problems (29–31). Importantly, the study findings also support the mediation hypothesis when examining CVD mortality and other causes of death, supporting prior research that shows the association between depression and mortality persists across a wide range of causes of death (8).

These longitudinal study findings are consistent with previous research by Everson-Rose and colleagues (5). Their study used data from Wave 1 of the ACLS and mortality follow-up through 1994 and found that the association between depressive symptoms at baseline and subsequent mortality risk is explained by baseline physical health conditions. A key strength of the study of Everson-Rose et al. and of this study is that both studies use a nationally representative sample of US adults. However, the study findings are not necessarily consistent with all prior research on this topic, which has shown mixed findings (4). For example, studies that use nationally representative samples have generally not found support for the independent hypothesis, whereas studies that use community samples or clinical samples have been more likely to show support for the independent hypothesis. One reason for this might be that much of the prior research on this topic instead relies on clinical samples or small community samples of older persons (4). In such samples, suicide rates, deaths from accidents (32), and depression tend to be significantly higher than in the general population. Such samples are also likely to be nonrepresentative of the population as a whole and may provide biased estimates.

This study is not without limitations. Although this is the first study to use longitudinal data with time-varying covariates, the long time lag between each wave of data (3–6 years) may lead to imprecision in the estimates. For instance, in the person-year data, respondents who report a CES-D score in 1986 are assumed to keep that score in 1987 and 1988, until they are again observed in 1989. This long time lag may be one reason for the lack of support for the spurious hypothesis. The long time lag between data points also prevents this study from testing more complex hypotheses about the depression-mortality association, such as the hypothesis that depression and physical health may influence mortality through complex feedback loops or interactions (16,33). Unfortunately, these data are not able to test such a hypothesis, and thus, these findings do not fully capture the complex, interactive, relationship between depression, health, and mortality. It would also be ideal if this study had the date of death, rather than just the year of death. Future research should collected annual data on depressive symptoms, physical health, and confounders over several years to further elucidate the link between depression and mortality. Despite its limitations, this study has many strengths. A unique strength is that it uses longitudinal data from the ACLS and uses measures of depressive symptoms, physical health, and other confounders at multiple points in time (1986, 1989, 1994, and 2002). Prior research has typically measured depressive symptoms, physical health, and confounders at one time point and has ascertained mortality status several years later. This has made it difficult for research to observe how the relationship between depressive symptoms, confounders, and mortality unfolds over time. To my knowledge, this study is the first to use multiple waves of data and is thus the first to be able to differentiate between the independent, spurious, and mediation hypotheses.

Furthermore, this is the first study, to my knowledge, to consider the role of stress process variables as potential confounders in the relationship between depression and mortality. Although life stress, social support, and personal coping resources did not explain the relationship, failing to adjust for these processes may artificially inflate the association between depression and mortality.

In sum, this study is the first to use nationally representative longitudinal data with repeated measures of depression, physical health, stress, and other confounders, to provide insight into the nature of the association between depression and mortality. The main strength of this study is the use of longitudinal data with time-varying measures of depression and confounders, allowing me to test competing hypotheses about how the

depression-mortality association unfolds over time. The main finding is that physical health mediates the association between depression and mortality. The study findings suggest that depression prevention and improving the health of people with depression may reduce the number of deaths attributable to depression in the population.

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REFERENCES

1. Wulsin LR, Evans JC, Vasan RS, Murabito JM, Kelly-Hayes M, Benjamin EJ. Depressive symptoms, coronary heart disease, and overall mortality in the Framingham Heart Study. Psychosom Med 2005;67:697–702.
2. Phillips AC, Batty D, Gale CR, Deary IJ, Osborn D, MacIntyre K, Carroll D. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam experience study. Psychosom Med 2009;71:395–403.
3. Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ. Association between depression and mortality in older adults. The Cardiovascular Health Study. Arch Intern Med. 2000;160:1761–8.
4. Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. Psychosom Med 1999;61:6–17.
5. Everson-Rose SA, House JS, Mero RP. Depressive symptoms and mortality risk in a national sample: confounding effects of health status. Psychosom Med. 2004;66:823–30.
6. Ferraro K, Nurridin TA. Psychological distress and mortality: are women more vulnerable? J Health Soc Behav 2006;47:227–41.
7. Zhang X, Norris SL, Gregg EW, Cheng YJ, Beckles G, Kahn HS. Depressive symptoms and mortality among persons with and without diabetes. Am J Epidemiol 2005;161:652–60.
8. Mykletun A, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R. Anxiety, depression, and cuase-specific mortality: the Hunt study. Psychosom Med 2007;69:323–31.
9. Wulsin LR. Does depression kill? Arch Intern Med 2000;160:1731–2.
10. MacLeod J, Davey Smith G, Heslop P, Metcalfe C, Carroll D, Hart C. Are the effects of psychosocial exposures attributable to confounding? Evidence from a prospective observational study on psychological stress and mortality. J Epidemiol Community Health 2001;55:878–84.
11. Rasul F, Stansfeld SA, Hart CL, Killis CR, Smith GD. Psychological distress, physical illness, and mortality risk. J Psychosom Res. 2004;57:231–6.
12. Pearlin L, Menaghan EG, Lieberman MA, Mullan JT. The stress process. J Health Soc Behav 1981;22:337–56.
13. Turner RJ, Lloyd DA. The stress process and the social distribution of depression. J Health Soc Behav. 1999;40:374–404.
14. Kessler RC. The effects of stressful life events on depression. Annu Rev Psychol 1997;48:191–214.
15. Lantz PM, House JS, Mero RP, Williams DR. Stress, life events, and socioeconomic disparities in health: results from the Americans' Changing Lives Study. J Health Soc Behav 2005;46:274–88.
16. Blazer DG, Hybels CF, Pieper CF. The association of depression and mortality in elderly persons. J Gerontol A Biol Sci Med Sci 2001;56:M505–9.
17. House JS. Americans' Changing Lives: Waves I, II, III, and IV, 1986, 1989, 1994, and 2002. Ann Arbor, MI: Inter-university Consortium for Political and Social Research; 2010.
18. House JS, Lantz PM, Herd P. Continuity and change in the social stratification of aging and health over the life course: evidence from a nationally representative longitudinal study from 1986 to 2001/2001 (Americans' Changing Lives Study). J Gerontol B Pschol Sci Soc Sci 2005;60:S15–26.
19. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
20. House JS. Americans' Changing Lives: Waves I, II, II, and IV, 1986, 1989, 1994, and 2002: Codebook. Ann Arbor, MI: Inter-University Consortium for Political and Social Research; 2008.
21. Pearlin LI. The sociological study of stress. J Health Soc Behav 1989;30:241–56.
22. Pearlin L, Schooler C. The structure of coping. J Health Soc Behav 1978;19:2–21.
23. John O. The Big Five Factor taxonomy: dimensions of personality in the natural language and questionnaires. In: Pervin LA, editor. Handbook of Personality: Theory and Research. New York: Guilford; 1990.
24. John O. Big Five Inventory (BFI-54). Berkeley: Institute of Personality and Research, University of California; 1991.
25. McRae RR, Costa PT. Personality, coping, and coping effectiveness in an adult sample. J Pers 1986;54:385–404.
26. Amirkhan JH, Risinger RT, Swickert RJ. Extraversion: a "hidden" personality factor in coping? J Pers 1995;63:189–212.
27. Singer JD, Willett JB. Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. Oxford: Oxford University Press; 2003.
28. Haukkala A, Konttinen H, Uutela A, Kawachi I, Laatikainen T. Gender differences in the associations between depressive symptoms, cardiovascular diseases, and all-cause mortality. Ann Epidemiol 2009;19:623–9.
29. Danner M, Kasl SV, Abramson JL, Vaccarino V. Association between depression and elevated C-reactive protein. Psychosom Med 2003;65:347–56.
30. Kaplan GA, Roberts RE, Camacho TC, Coyne JC. Psychosocial predictors of depression: prospective evidence from the human population laboratory studies. Am J Epidemiol 1987;125:206–20.
31. Roberts RE, Kaplan GA, Shema SJ, Strawbridge WJ. Prevalence and correlates of depression in an aging cohort: the Alameda County Study. J Gerontol B Pschol Sci Soc Sci 1997;52B:S242–58.
32. Roberts RE, Kaplan GA, Camacho TC. Psychological distress and mortality: evidence from Alameda County. Soc Sci Med 1990;31:527–36.
33. Schulz R, Martire LM, Beach SR, Scheier MF. Depression and mortality in the elderly. Curr Dir Psychol Sci 2000;9:204–8.