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; for the SHEP Cooperative Research Group

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).

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.

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From the Albert Einstein College of Medicine, Bronx, NY (Drs Wassertheil-Smoller and Chang); University of Tennessee, Memphis (Dr Applegate); Mayo Medical School, Rochester, Minn (Dr Berge); University of Texas Health Science Center at Houston (Dr Davis and Ms Pressel); University of Minnesota, Minneapolis (Dr Grimm); University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, New Brunswick (Dr Kostis); and the National Institutes of Health, Bethesda, Md (Ms Schron). A list of the participating centers and investigators of the Systolic Hypertension in the Elderly Program (SHEP) appears on pages 559 and 560.

STUDIES OF the relationship of antecedent depression to cardiovascular disease or mortality have not reported consistent results. Some studies on patients with major clinical depression have reported increased mortality.[1,2] However, a question with broader medical and public health implications concerns the effect of depressive symptoms or depressed mood that does not in itself merit a clinical diagnosis of depression. It has been estimated that 11% and 19% of elderly community–dwelling men and women, respectively, score above the cutoff point for being at high risk of clinical depression on the commonly used self-report Center for Epidemiological Studies–Depression (CES-D) scale.[3] Other studies on elderly people have reported similar or higher proportions.[4-6] The prospective studies on this issue have provided contradictory findings. Several studies have found a positive relationship between depression and subsequent cardiovascular events.[1,2,7-9]; others have not.[10] Some of these studies have used only one measurement of depressive symptoms as a predictor. A recent study by Thomas et al[10] on community-dwelling elderly people measured depression twice (2 years apart) using the CES-D scale, which defined persons with transient depression as those scoring above the cutoff point of 16 on only one occasion, and which defined persons with

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METHODS

ENROLLMENT

The SHEP was a randomized placebo-controlled clinical trial of treatment of isolated systolic hypertension conducted in 16 clinical centers across the United States. The SHEP design has been described in detail elsewhere.[11] In summary, 4736 men and women aged 60 years or older with isolated systolic hypertension were randomized to receive active treatment with low-dose antihypertensive drugs or matching placebo. A stepped-care approach was used starting with chlorthalidone at 12.5 mg/d, and adding atenolol at 25 mg/d if necessary, to achieve the goal BP that was a systolic BP of less than 160 mm Hg or 20 mm Hg less than the entry level systolic BP, whichever was lower. To be eligible for randomization, participants had to have a baseline systolic BP of 160 mm Hg or more and less than 220 mm Hg, and a diastolic BP of less than 90 mm Hg. Blood pressure eligibility for randomization was determined by using the average of four seated BP measurements, two at each of two baseline visits. Persons receiving antihypertensive medication at the initial screening contact were withdrawn from their antihypertensive medication with informed consent and approval of their personal physicians, and if they met eligibility criteria within 8 weeks of not receiving medication, they were randomized into the trial. Exclusion criteria included the presence of major cardiovascular disease or other major disease conditions such as cancer, alcoholic liver disease, renal dysfunction, or the presence of medical management problems. All participants had quarterly visits at which BP, heart rate, body weight, medical history, and review of medication use were obtained, and annual visits at which a more detailed medical history, complete physical examination, and laboratory tests were performed. Questionnaires for depression and dementia were administered semiannually.

ASSESSMENT OF DEPRESSION

Depressive symptoms were assessed with two screening scales: the Short-Care Depressive Symptoms Scale[14] and the CES-D scale.[15] The Short-Care Depressive Symptoms Scale was in the form of a semistructured interview in which trained raters assessed a variety of symptoms. If participants reached the prespecified cutoff point of seven or more points on the Short-Care Depressive Symptoms Scale, the scale was administered again at the next quarterly visit and if the patient reached the cutoff point at any two consecutive quarterly visits, he or she was referred to a psychologist or psychiatrist for clinical evaluation of depression. The correlation coefficient between these two scales was .67 at baseline and .76 at 5 years.

The CES-D scale is widely used and consists of 20 questions in which respondents are asked how often they have experienced certain feelings or symptoms during the past week. They may respond on a four-point scale from rarely (0) to almost always (3). The reliability of the CES-D scale ranges from 0.77 to 0.92 for various measures of reliability and for different populations.[15] Persons with scores of 16 or more on the CES-D scale were considered "possibly depressed." This cutoff point of 16 or more on the CES-D scale is widely used as a screening tool,[3,6,10,15] indicating that depressive symptoms have reached a level where clinical diagnosis of depression is more likely. The complete scale is given in **Table 1**. The results presented herein are based on the CES-D scale.

END-POINT DEFINITIONS

The end points considered herein are (1) deaths from all causes, (2) fatal and nonfatal strokes, and (3) fatal and nonfatal myocardial infarction (MI). Nonfatal stroke was defined as the rapid onset of new neurologic deficit attributed to obstruction or rupture in the arterial system and persisting for at least 24 hours unless death supervened. Nonfatal stroke was confirmed by the neurologic findings from examination or brain scan. Fatal

persistent depression as those scoring above the cutoff point on both measurement occasions. It was found that baseline, transient, or persistent depression did not predict mortality. However, the subsequent observation period was only 12 months; although there were 1855 participants, there may not have been sufficient power to detect meaningful effects in that short period. The question of emerging depressive symptoms over time in relation to the risk of cardiovascular or mortal events has not been addressed in population-based studies until now.

We report herein on findings from the Systolic Hypertension in the Elderly Program (SHEP), on the relationship between *changes* in depressive symptoms over time and cardiovascular events among elderly men and women aged 60 years or older. The SHEP was a randomized placebo-controlled double-blind clinical trial of antihypertensive therapy in participants who were followed up for 5 years and had depression scales administered every 6 months.[11]

The objectives of SHEP were to determine if antihypertensive treatment would reduce total strokes in men and women aged 60 years or older with isolated systolic hypertension (defined as a systolic blood pressure [BP] of ≥160 mm Hg and a diastolic BP of <90 mm Hg). The positive findings in the treated group have broad implications for public health in that stroke incidence was reduced by 36%, coronary heart disease by 27%, and total cardiovascular disease by 31%.[12] The benefit of treatment was apparent in all age groups including those older than 80 years. To determine if active treatment or placebo was associated with any adverse effects with respect to depression or dementia, an extensive behavioral battery was incorporated into the study design. The SHEP found no difference in incidence of dementia or depression between the treated and placebo groups.[12,13] The question our report addresses is whether depression and *change* in depressive symptoms are prospectively associated with risk of cardiovascular or mortal events in the total SHEP cohort as well as in the placebo and treatment groups separately.

stroke was established from death certificates or autopsy reports and included preterminal hospitalization data. Sudden cardiac death was defined as a death witnessed within 1 hour after the onset of severe cardiac symptoms or within 1 hour after the subject was last seen without symptoms and no known nonatherosclerotic or other event that could explain the sudden death and no documentation of acute MI in the 4 weeks before death. A nonfatal MI was defined as typical symptoms of acute MI plus either typical electrocardiographic changes or significant enzyme level elevations, but not including silent MI. Fatal MI was established at autopsy or on death certificate, also using preterminal hospitalization data. Occurrence of nonfatal and fatal events was confirmed by a panel of three physicians blinded to randomization status and included two neurologists for neurologic events and one cardiologist for cardiac events.

STATISTICAL METHODS

Cox proportional hazards regression analyses that account for both time-constant and time-dependent covariates were used to examine the relationship between change in CES-D score over time and the selected outcomes. Time-constant covariates are baseline variables that do not change over time, such as sex or race; time-dependent variables are those, like depression scores, that may change during the course of the trial. This type of life-table analysis controls for unequal periods of observation for different individuals, permits statistical adjustment for baseline covariates, and accounts for changes in depression scores over the time of the trial.

Baseline variables included in the model were age, race, sex, years of education, and histories of MI, stroke, and diabetes, and current smoking status. Time-dependent variables (measured at 6 months and every 6 months thereafter) were change in depression score from baseline and change in activities of daily living (ADL) scale,[16] which is an index of disability administered annually. An interaction term between change in depression score and sex was also entered to determine if the risk of events associated with a change in depressive symptoms differed for men and women. For analyses of the end-point death, the occurrence of stroke or MI was entered as a time-dependent variable to control for possible depression after MI or stroke. Although the change scores were approximately normally distributed, we also used log-transformed scores in the analyses. Applicability of the proportional hazards regression model was tested and met by plotting $\log\{-\log[S(t)]\}$ as a function of $\log(t)$ where $S(t)$ is the survival function.[17] Relative risks derived from the Cox regression analyses are presented per 5-unit increase in the CES-D score. The within-person SD on the CES-D scale in our cohort was 3.4. Thus, a five-point increase in the CES-D score for an individual represents an increase of approximately 1.5 SDs above his or her mean. A five-point increase has been used in other studies as an indication of change.[10]

PARTICIPANTS INCLUDED IN THE ANALYSES

Participants in the SHEP who had not had one of the specified outcomes by 6 months and who had valid baseline values for depression scores were included in analyses pertaining to baseline predictors of events after the first 6 months (n=4508). Thus, of the 4736 participants randomized to SHEP, 228 were excluded for these analyses. The reasons for these 228 exclusions were as follows: 121 had missing baseline CES-D scores, 33 had fatal or nonfatal stroke, 18 had fatal or nonfatal MI, 39 had a new cancer diagnosis, and 17 died of causes other than stroke or MI before 6 months. Of the remaining 4508 participants, 141 had only a baseline depression score and no subsequent CES-D scores against which to measure change and they were excluded from analyses involving change in depression, leaving 4367 persons available for Cox regression analyses that were concerned with depression as a time-dependent variable. If a depression score was missing at a subsequent visit, the most recent available depression score was substituted.

RESULTS

BASELINE CHARACTERISTIC OF COHORT

The mean age of the participants was 72 years and 13.1% were 80 years or older. Black men composed 4.6% of the group; black women, 9.3%; white men, 35.2%; and white women, 43.9%. At the initial contact, 33% of the participants were receiving antihypertensive medication; 61% had baseline electrocardiographic abnormalities. The mean baseline systolic and diastolic BPs were 170 mm Hg and 77 mm Hg, respectively. These variables were similar to the whole cohort of 4736 participants,[12] and the actively treated group and placebo group were similar in all baseline characteristics examined.

BASELINE DEPRESSIVE SYMPTOMS

Table 2 shows depression scale scores at baseline. The mean CES-D score for the total group was 4.15, which is lower than that from other samples of the elderly population, such as the Yale Health and Aging Project, where the average score for white persons was about 8.1.[3] Women had significantly higher depression scores than men. There was significant variation by race and ethnicity, with black and Hispanic participants having higher CES-D scores than whites and with Asians having the lowest mean score. There was a small but significant rise in mean depression scores with age, but the average baseline depression scores were still low even among those older than 80 years (mean score, 5.16). Women scored significantly higher within each age group with a P value less than .01 (data not shown).

The overall baseline prevalence of depression (defined as a CES-D score ≥ 16) was 4.8% for the entire cohort, and about twice as high for women as for men (6.2% vs 2.8%, $P \leq .001$). A substantially higher proportion of blacks and Hispanics (8.9% and 9.8%, respectively) scored above the cutoff point than did whites (4.0%) or Asians (3.6%). Within each race and ethnic group, a higher proportion of women than men scored above the cutoff point, in particular among the black participants, where the pro-

Table 1. Center for Epidemiological Studies–Depression Scale*

Using the scale below, indicate the number that best describes how often you felt or behaved this way—during the past week

1. I was bothered by things that usually don't bother me
2. I did not feel like eating; my appetite was poor
3. I felt that I could not shake off the blues even with help from my family or friends
4. I felt that I was just as good as other people†
5. I had trouble keeping my mind on what I was doing
6. I felt depressed
7. I felt that everything I did was an effort
8. I felt hopeful about the future†
9. I thought my life had been a failure†
10. I felt fearful
11. My sleep was restless
12. I was happy†
13. I talked less than usual
14. I felt lonely
15. People were unfriendly
16. I enjoyed life†
17. I had crying spells
18. I felt sad
19. I felt that people disliked me
20. I could not get "going"

*The four-point scale is as follows: 0 = rarely or none of the time (<1 day); 1 = some or a little of the time (1 to 2 days); 2 = occasionally or a moderate amount of time (3 to 4 days); and 3 = most or all of the time (5 to 7 days).

†Reverse scoring.

portion of women scoring as possibly depressed was about three times higher than that for black men (11.7% vs 3.4%).

INCIDENCE OF DEPRESSION

Table 3 shows the percent of the cohort who at baseline had a CES-D score below the cutoff point of 16, but who at some time during the trial scored 16 or more. The overall 5-year incidence of depression in this cohort was similar in the actively treated and placebo groups (12.4% and 12.5%, respectively, over 5 years).

Women (14.9%), however, had a significantly higher incidence of becoming depressed than men (9.3%; $P \leq .001$ for both women and men). The rates of clinically diagnosed depression were approximately one third the rates of depression as defined on the CES-D scale (3.5% for women and about 5.5% for men), with no differences between drug and placebo groups either in men or women.

INCIDENCE OF EVENTS BY DEPRESSED STATUS AT BASELINE

Baseline depression (CES-D score, ≥16) did not predict the occurrence of subsequent stroke, MI, or death from any cause over the next 5 years, with approximately the same proportions of the depressed (20.9%) and not depressed (18.0%) developing any of these events ($P=.27$; **Table 4**). This finding was the same in a Cox proportional hazards analysis after controlling for all the baseline covariates.

Table 2. Baseline Depression Scores*

	n	CES-D Scale Score: Mean	CES-D Scale Score: Percent ≥16
Total group	4506	4.15 (SD 5.42)	4.8
Sex			
Men	1936	3.33†	2.8†
Women	2572	4.77	6.2
Race and ethnicity	3564	3.84†	4.0†
White			
Black	628	5.91†	6.9
Asian	195	3.13	3.6
Hispanic	82	6.70	9.8
Other	39	4.56	5.1
White			
Men	1585	3.19†	2.7‡
Women	1979	4.36	5.0
Black			
Men	208	4.36†	3.4‡
Women	420	6.69	11.7
Asian			
Men	91	2.68	2.2
Women	104	3.53	4.8
Hispanic			
Men	36	5.19§	8.3
Women	46	7.87	10.9
Other			
Men	16	3.44	0.0
Women	23	5.35	8.7
Age, y			
60-69	1696	3.86†	4.5
70-79	2020	4.14	4.7
80+	592	5.16	5.9
Treatment			
Active	2252	4.16	4.6
Placebo	2256	4.15	5.0

*CES-D indicates Center for Epidemiological Studies–Depression. The P values are comparisons between and among groups within a category.

†$P \leq .0001$.

‡$P \leq .001$.

§$P \leq .05$.

COX REGRESSION ANALYSES

Since this was a prospective study and since depression scores change over time, we performed Cox proportional hazards analyses controlling for covariates and with change in depression as a time-dependent covariate. In addition, because depressive symptoms may be related to disability that in turn may be related to an impending event, correlation coefficients were determined between ADL scale and the CES-D scale. The correlation coefficients, though significantly different from zero, were quite low and ranged from −.11 at baseline to −.20 among the survivors at 5 years that accounted for no more than 1% to 4% of the variance in the CES-D score. The negative correlation coefficient indicates increased depression scores with decreasing ADL scores, though it does not indicate whether loss of function with aging or illness leads to depression or vice versa. However, since there was an increase in the correlation coefficients over time, the ADL scale was included as a time-dependent covariate in multivariate analyses. Baseline ADL scale scores alone would not be able to

Table 3. Incidence of Possible Depression During Follow-up Defined as Scoring Above the Cutoff Point of ≥16 on the CES-D Scale*

	CES-D Scale	
	No.†	Percent ≥16‡
Total group not depressed at baseline	4293	12.4
Sex		
Men	1881	9.3§
Women	2412	14.9
Race and ethnicity		
White	3422	12.5‖
Black	572	14.0
Asian	188	7.5
Hispanic	74	17.6
Other	37	2.7
White		
Men	1542	9.5§
Women	1880	14.9
Black		
Men	201	8.0¶
Women	371	17.3
Asian		
Men	89	6.7
Women	99	8.1
Hispanic		
Men	33	15.2
Women	41	19.5
Other		
Men	16	6.3
Women	21	0.0
Age, y		
60-69	1811	10.7‖
70-79	1925	13.5
80+	557	14.5
Treatment		
Active	2149	12.4
Placebo	2144	12.5

*CES-D indicates Center for Epidemiological Studies–Depression. The P values are comparisons between groups within a category.

†Persons having CES-D score at baseline of less than 16.

‡Percent of number scoring above cutoff point at any time during trial after baseline.

§$P \leq .0001$.

‖$P \leq .05$.

¶$P \leq .001$.

account for possible effects of deterioration of functions with aging. The primary variable of interest was change in depressive symptoms on the CES-D scale as a time-dependent covariate, while controlling for baseline depression, age, sex, race, randomization group, years of education, history of stroke, MI, or diabetes, smoking, baseline ADL, and ADL as a time-dependent covariate.

Table 5 shows the relative risk of events associated with a 5-unit increase on the CES-D scale. There was a 25% increase in risk of death per each 5-unit increase in depression on the CES-D scale (relative risk, 1.25; 95% confidence interval, 1.15 to 1.36; $P<.001$). In the regression model for death, the occurrence of a stroke or MI was entered as an additional covariate to control for the possible confounding effect of increased depression after such nonfatal events. The significantly increased risk of death with increase in depressive symptoms held true for women as well as men and in the treated group as well as in the placebo group.

Table 4. Incidence of Events for Those Depressed at Baseline (CES-D Score ≥16) and Those Not Depressed (CES-D Score <16)*

Event	Baseline <16 (n=4293), %	CES-D Score ≥16 (n=215), %
Any event	18.0	20.9
MI	3.1	2.8
Stroke	4.9	4.2
Cancer	6.6	7.0
Death	8.6	9.8

*Comparing those with baseline Center for Epidemiological Studies–Depression (CES-D) of less than 16 vs 16 or more. MI indicates myocardial infarction.

There was a similar increase in risk of either stroke or MI, controlling for sex and the other covariates (relative risk, 1.18; 95% confidence interval, 1.08 to 1.30; $P \leq .001$). The likelihood ratio test comparing the model that included change in the CES-D score to the reduced model without the time-dependent variable of change in depressive symptoms indicated a significant, independent effect of increase in depression as a risk factor ($P=.001$). When men and women were analyzed separately, there was an excess risk of 26% per 5-unit change in CES-D score among women ($P \leq .001$) and a nonsignificantly elevated risk in men.

Models considering the end points of stroke and MI separately indicate that the risk of stroke controlling for MI was significantly associated with an increase in depression, particularly among women, and risk of MI (controlling for prior occurrence of stroke) was also increased, but not significantly.

COMMENT

In a large prospective follow-up study of men and women older than 60 years with isolated systolic hypertension, our findings from SHEP show that an increase in depressive symptoms is associated with increased risk of death and stroke, particularly among women. These findings pertain to persons who exhibit changes in depression on the commonly used CES-D scale, and who are community-dwelling persons rather than patients diagnosed as having clinical depression that meets psychiatric criteria. Other than having isolated systolic hypertension, the patients at the start of SHEP were generally a healthy group of individuals, both physically and psychologically. Thus, the implications of these findings relate to a potentially large group of persons.

The SHEP cohort at the inception of the study showed a low level of depressive symptoms, even at older ages. Women, blacks, Hispanics, and the less educated reported more depressive symptoms at baseline than other sociodemographic groups. We found that after controlling for multiple covariates that included a time-dependent measure of disability, an increase of five points on the CES-D scale was associated with a 25% increase in risk of death and an 18% increase in risk of stroke for the cohort of individuals who were free of events during the first 6 months after baseline. An increase of 5 units rep-

Table 5. Relative Risk of Event per 5-Unit Increase in CES-D Score*

Event	Group	N	n	RR	95% CI	P
Death	All	4367	355	1.26	1.16-1.36	<.001
	Women	2483	165	1.18	1.05-1.33	.006
	Men	1884	190	1.32	1.19-1.47	<.001
	Placebo	2167	178	1.35	1.21-1.50	<.001
	Treatment	2200	177	1.17	1.03-1.32	.02
Stroke or MI	All	4367	321	1.18	1.08-1.30	<.001
	Women	2483	165	1.26	1.12-1.42	<.001
	Men	1884	156	1.07	0.91-1.25	.43
	Placebo	2167	193	1.15	1.01-1.30	.03
	Treatment	2200	128	1.24	1.07-1.42	.003
Stroke	All	4367	204	1.21	1.08-1.35	.001
	Women	2483	117	1.29	1.13-1.48	<.001
	Men	1884	87	1.06	0.86-1.30	.59
	Placebo	2167	125	1.18	1.02-1.36	.03
	Treatment	2200	79	1.26	1.06-1.49	.01
MI	All	4367	126	1.14	0.97-1.34	.11
	Women	2483	55	1.20	0.97-1.48	.09
	Men	1884	71	1.07	0.83-1.38	.61
	Placebo	2167	73	1.14	0.91-1.41	.25
	Treatment	2200	53	1.15	0.90-1.47	.26

CES-D indicates Center for Epidemiological Studies–Depression; RR, relative risk; CI, confidence interval; and MI, myocardial infarction.

resents approximately 1.5 SDs above the patient's mean. About 37% of the patients had an increase of 5 units or more from baseline at some time during the trial and before any event, after excluding all patients who had a diagnosis of cancer during the trial. Approximately 9% had an increase of five points or more on the CES-D scale during the first 6 months.

The incidence of possible depression during the trial, defined as exceeding a cutoff-point level of 16 or more on the CES-D scale among those who scored below the cutoff point at baseline was 12.4%, and there was no difference between the treated and placebo groups. A comparable incidence rate (11.2%) was found in a study of 1457 elderly community–dwelling residents.[18] However, similar to the findings on baseline prevalence, the incidence was considerably higher in women than in men. Other studies have also found a higher prevalence or incidence of depression among women[3,5,6,19] and among blacks,[5,19] as well as among the less educated.[5,20,21] The low prevalence and incidence of depression that we found among Asians is intriguing.

Patients with affective disorder have been reported to have a higher-than-expected rate of mortality from cardiovascular disease.[2] Depression, assessed through a variety of instruments, was associated with mortality in several studies[22,23] but not in others.[10,24-26] In one of the first prospective psychiatric studies by Crisp et al[27] of the mental precursors to MI, male patients who in the future developed coronary heart disease were found to be significantly more depressed than the other male subjects. In a prospective study by Appels and Mulder[28,29] of 3877 male civil servants in the Rotterdam Civil Servants Study, it was found that only selected elements of depression were found before MI. Two major elements of depression, negative self-concept and feelings of guilt, were not found to be predictive in the Rotterdam Civil Servants Study. The other depressive symptoms (a sad, apathetic mood, loss of sleep and sexual desire, fatigue, and tiredness) were called "vital exhaustion." Appels and Mulder suggest that vital exhaustion is not necessarily a cause of coronary heart disease but may promote its progression in persons already prone to it.

The study by Thomas and colleagues[10] of elderly persons with an average age of about 75 years reported that respondents with either incident depression over 2 years of follow-up or persistent symptoms of depression (ie, scoring above the CES-D scale cutoff point of 16 both at baseline and at 2 years) were not more likely to die in the following year, nor did baseline depression predict mortality, while poor or declining health was a predictor. In our study, ADL as an indication of disability was not predictive of mortality, whereas an increase in depression was predictive. The study by Thomas et al was smaller (1855 participants compared with 4367 in our study), had a shorter follow-up (1 year compared with 5 years in SHEP), and did not look at depression as a time-dependent covariate. These factors may account for the discrepancy.

The Yale Health and Aging Project[24] (a study of 2604 stroke-free men and women in New Haven, Conn, with a mean age of 74 years and with 7 years of follow-up) found that while the CES-D scale predicted stroke in a univariate Cox proportional hazards model, it had no effect after controlling for age, smoking, diabetes, hypertension, and physical function. In contrast, we found that there was an 18% increase in risk of stroke overall and a 29% increase among women for a 5-unit increase on the CES-D scale, after controlling for multiple covariates that included changes in disability levels over time. All of our participants had isolated systolic hypertension, and the increase in risk with increasing depression was significant in both the treated and placebo groups. The data presented herein do not prove a causal pathway leading from depression to cardiovascular events. It is possible that the development of premonitory signs and symptoms of cardiovascular events, eg, increasing angina or dyspnea, could have led to increased depressive scores.

Albert Einstein College of Medicine, Bronx, NY

M. Donald Blaufox, MD, PhD (*principal investigator*); William H. Frishman, MD; Maureen Magnani, RN; Gail Miller, RN; Zirel Sweezy; and Sylvia Wassertheil-Smoller, PhD.

Emory University School of Medicine, Atlanta, Ga

W. Dallas Hall, MD (*principal investigator*); Sandy Biggio, RN, BSN; Margaret Chiappini, RN, BSN; Con Hamilton; Margaret Huber, RN, BSN; Gail McCray; Deanne J. Unger, RNC, BSN; and Gary L. Wollam, MD.

Kaiser Permanente Center for Health Research, Portland, Ore

Thomas M. Vogt, MD, MPH (*principal investigator*); Merwyn R. Greenlick, PhD; Stephanie Hertert; Patty Karlen, RN; Marlene McKenzie, RN, MN; Marcia Nielsen, RN, MN; Kathy Reavis, RN; and Vicki Wegener, RN, FNP.

Medical Research Institute of San Francisco, San Francisco, Calif

William McFate Smith, MD, MPH (*principal investigator*); Geri Bailey, RN; Philip Frost, MD; Jean Maier, RN; Ann Slaby; and Jacqueline Smith, RN.

Miami Heart Institute, Miami, Fla

Fred Walburn, PhD (*principal investigator*); Maria Canosa-Terris, MD; Garcia Garrison, RN; Maria Gutierrez, MD; Melissa Jones; Jeff Raines, PhD; Naldi Ritch; Avril Sampson, MD; Elisa Serantes, MD; and Susan Surette.

Northwestern University Medical School, Chicago, Ill

David Berkson, MD (*principal investigator*); Flora Gosch, MD; Joseph Harrington; Patricia Hershinow, RN; Josephine Jones; Angeline Merlo; and Jeremiah Stamler, MD.

Pacific Health Research Institute, Honolulu, Hawaii

Helen Petrovitch, MD (*principal investigator*); Sandra Akina, RN; J. David Curb, MD, MPH; Fred I. Gilbert, MD; Mary Hoffmeier, RN; and Lei Honda-Sigall, RN.

Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway

John B. Kostis, MD (*principal investigator*); Nora Cosgrove, RN; Susan Krieger, RN; and Clifton R. Lacy, MD.

University of Alabama, Birmingham

Richard M. Allman, MD (*principal investigator*); Ralph E. Allen, PAC; Donna M. Bearden, MD; Lisa Carlisle; Vanessa P. Cottingham; Laura Farley, RN; Julia Hall; Glenn H. Hughes, PhD; Phillip Johnson; Linda Jones, CRNP; Laverne Parr; Pat Pierce; and Harold W. Schnaper, MD.

University of California, Davis

Nemat O. Borhani, MD, MPH (*principal investigator*); Patty Borhani; Alfredo Burlando, MD; Frances LaBaw, RN; Sheila Lame; Marshall Lee, MD; and Susan Pace, RN.

University of Kentucky Medical Center, Lexington

Gordon P. Guthrie, Jr, MD (*principal investigator*); Jenny Brown; Jimmie Brumagen, RN; Ellen Christian, PAC; Lynn Hanna, PAC; Arlene Johnson, PhD; Jane Kotchen, MD; Theodore Kotchen, MD; William Markesbery, MD; Rita Schrodt, RN; and John C. Wright, MD.

University of Minnesota, Minneapolis

Richard H. Grimm, MD, PhD (*principal investigator*); Julie Levin; Mary Perron, RN; and Alice Stafford.

University of Pittsburgh, Pittsburgh, Pa

Lewis H. Kuller, MD, DrPH (*coprincipal investigator*); Robert McDonald, MD (*coprincipal investigator*); Shirley Arch (deceased); Betsy Gahagan, RN; Jerry Noviello, PhD; and Gale Rutan, MD.

University of Tennessee, Memphis

William B. Applegate, MD, MPH (*principal investigator*); Laretha Goodwin, RN, MBA; Stephen T. Miller, MD; Amelia Rose, RN; and Alice Wallace, RN.

Washington University, St Louis, Mo

H. Mitchell Perry, Jr, MD (*principal investigator*); Greta H. Camel, MD ; Sharon Carmody; Jerome Cohen, MD; Judith Jensen, RN; and Elizabeth Perry.

Yale University, New Haven, Conn

Henry R. Black, MD (*principal investigator*); Diane Christianson, RN; Janice A. Davey, MSN; Charles K. Francis, MD; and Linda Loesche.

School of Public Health, University of Texas Health Science Center at Houston, Coordinating Center

C. Morton Hawkins, ScD (*principal investigator*); Barry R. Davis, MD, PhD; William S. Fields, MD; Darwin R. Labarthe, MD, PhD; Lemuel A. Moye, MD, PhD; Sara Pressel, MS; and Richard B. Shekelle, PhD.

Program Office, National Heart, Lung, and Blood Institute, Bethesda, Md

Project officer: Jeffrey L. Probstfield, MD; *deputy project officer*: Eleanor Schron, RN, MS; *former project officers*: Jeffrey A. Cutler, MD, MPH, Curt Furberg, MD, PhD; *biostatistics officers*: Edward Lakatos, PhD, Janet Wittes, PhD; *contracting officer*: C. Eugene Harris; *contract specialist*: Linda Gardner; *other key personnel*: Thomas P. Blaszkowski, PhD, Clarissa Wittenberg, MSW.

Continued on next page

Various mechanisms have been suggested to link depression and coronary heart disease.[1] Two main avenues are through the effects of depression on lipid metabolism and through altered sympathetic arousal in patients with depression.[1,30] Free fatty acids increase because of decreased glucose utilization and raised steroid production, both of which are associated with depression.[31-36] It has been reported that there is raised autonomic sympa-

National Institute on Aging, Bethesda, Md

Evan Hadley, MD; J. David Curb, MD, MPH; Jack Guralnik, MD, PhD; Lot Page, MD (deceased); Teresa Radebaugh, ScD; Stanley Slater, MD; and Richard Suzman, PhD; Steering Committee: Kenneth G. Berge, MD, Mayo Clinic, Rochester, Minn (*chair*); Behavioral Assessment Subcommittee: William B. Applegate, MD, MPH (*chair*); Clinic Coordinators Subcommittee: Judith Jensen, RN (*chair*); and Drug Selection Working Group: Robert McDonald, MD (*chair*); Endpoints and Toxicity Subcommittee: H. Mitchell Perry, Jr, MD (*chair*); Operations and Medical Care Subcommittee: Thomas M. Vogt, MD, MPH (*chair*); Publications and Presentations Subcommittee: Jeremiah Stamler, MD (*chair*); Recruitment and Adherence Subcommittee: Nemat O. Borhani, MD, MPH (*chair*); Recruitment Coordinators Working Group: Joseph Harrington (*chair*); Scientific Review and Ancillary Studies Subcommittee: W. Dallas Hall, MD (*chair*); and Executive Committee: Kenneth G. Berge, MD (*chair*). The Data and Safety Monitoring Board members are: James C. Hunt, MD (*chair*), University of Tennessee; C. E. Davis, PhD, and Herman A. Tyroler, MD, University of North Carolina, Chapel Hill; Ray W. Gifford, Jr, MD, Cleveland Clinic Foundation, Cleveland, Ohio; Millicent W. Higgins, MD, National Heart, Lung, and Blood Institute; Adrian M. Ostfeld, MD, Yale University School of Medicine; John W. Rowe, MD, Mt Sinai Medical Center, New York, NY; K. Warner Schaie, MD, Pennsylvania State University, State College, Pa; Jack P. Whisnant, MD, Mayo Clinic; and Joseph A. Wilber, MD, Atlanta.

Health Care Financing Administration, Washington, DC

William Merashoff.

Drug Distribution Center, Perry Point, Md

Richard Moss.

Central Chemical Laboratory, MetPath Laboratories, Teterboro, NJ

S. Raymond Gambino, MD; Arlene Gilligan; Joseph E. O'Brien, MD; Nicholas Scalfratto; and Elana Sommers.

Electrocardiographic Laboratory, University of Minnesota

Richard Crow, MD; Margaret Bodellan; and Ronald J. Prineas, MB, PhD.

Computed Tomogram Reading

L. Anne Hayman, MD, Baylor College of Medicine, Houston, Tex; C. V. G. Krishna Rao, MD, University of Maryland, Baltimore; *consultants*: Marilyn Albert, PhD, Harvard Medical School and Massachusetts General Hospital, Boston; Lisa F. Berkman, PhD, Yale University; Judith Challop-Luhr, PhD, Floral Park, NY; Debra Egan, MS, MPH, Washington; June Gregonis, Duke University Medical Center, Durham, NC; Thomas R. Price, MD, University of Maryland Hospital, Baltimore; Ronald J. Prineas, MB, PhD, University of Miami; Kenneth A. Schneider, MD, Duke University Medical Center; Philip Weiler, MD, University of California at Davis; and Janet Wittes, PhD, Washington.

thetic activity in patients with depression,[29,37] and angiography has shown that there is a correlation between depression and vessel obstruction.[38] A link between depression and sudden death has been postulated to operate through the interaction of the catecholamine-corticoid systems.[7,39,40] An acute catecholamine surge is associated with arrhythmia during the first hours following an MI.[41] Also, the serotonergic system, which is important in depression, may be implicated in arrhythmia.[42]

Links can also be made between life circumstances and the evidence that lipid and sympathetic systems are more active under situations of stress.[1,39] It has been found that especially patients dying of MI experienced one or more periods of distress, exhaustion, or depression in their lives. In the Rotterdam Civil Servants Study,[28,29] it was found that memories of earlier periods of mental and physical exhaustion are reactivated before MI. Many patients with coronary artery disease stated that their mental state before their MI was similar to an earlier time in which they had been "overwrought."[9]

An increase in depressive symptoms preceding stroke, MI, or death may be a marker for an impending event. In the analyses presented herein, we did not relate change in depression to change in premonitory signs and symptoms of cardiovascular disease events, such as unstable angina or transient ischemic attacks. If an increase in depression occurred subsequent to the appearance of premonitory symptoms but antecedent to the event, it would suggest that the premonitory symptoms caused the depression. In such a case, the increase in depression could be an alert that some acute morbid event may be on its way. On the other hand, if the increase in depression occurred antecedent to the appearance of premonitory symptoms that in turn were antecedent to the event, then the depression might be a causal factor. In our study, we cannot ascertain what causal pathways may be operating. Subtle presentations of impending acute events related to chronic disease may cause depression. Conversely, depression may cause subtle perturbations in neurohumoral function that serve as the "straw that breaks the camel's back" in terms of helping precipitate an acute event in a patient with a chronic disease. There are three possibilities for the observed association between an increase in depression scores and stroke, MI, and total mortality: (1) the increase in depressive symptoms is the cause of the subsequent stroke, MI, or death; (2) the impending stroke, MI, or underlying cause of death causes the increase in depressive symptoms; and (3) some other factor or process causes both the depressive symptoms and the occurrence of stroke, MI, or death.

Increasingly, primary care physicians will be the gatekeepers of health care services for all patients and for the growing number of older patients. The Agency for Health Care Policy and Research at the US Department of Health and Human Services has published clinical practice guidelines for the detection, diagnosis, and treatment of depression in primary care[43,44] and is beginning to evaluate the extent to which these guidelines are followed. However, these guidelines mostly pertain to major mood disorder and not to the much more common and milder aspects of depressive symptoms that are the focus of our study. Our

findings emphasize that physicians should recognize signs of increasing depression in elderly patients and suggest that standardized assessments of depressive symptoms in clinical practice may be useful as a nonspecific, but perhaps sensitive, premonitory warning of the possible occurrence of an acute morbid event on top of a silent (or stable) chronic disease. In particular, women's self-reported symptoms of changes in mood or affect may be too readily dismissed as not clinically significant, though such changes are associated with increased risk of untoward events that perhaps could be prevented by appropriate and timely intervention. Nevertheless, a limitation of our study is that it addresses a post hoc hypothesis and needs to be replicated before such widespread screening of depressive symptoms is adopted in clinical practice.

In summary, among elderly persons with isolated systolic hypertension, we found a significant and substantial excess risk of death, stroke, or MI associated with an increase in symptoms of depression over time after controlling for multiple covariates. Studies are needed to establish if there is a causal relationship, to elucidate mechanisms that link depression to stroke or death, and to determine if intervening in possible depression may decrease the risk of these events.

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Reprint requests to the Albert Einstein College of Medicine, Department of Epi/Soc Med-1312 Belfer, 1300 Morris Park Ave, Bronx, NY 10461 (Dr Wassertheil-Smoller).

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