ORIGINAL INVESTIGATION

Depression and Cardiovascular Sequelae in Postmenopausal Women

The Women's Health Initiative (WHI)

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Background: Subclinical depression, often clinically unrecognized, may pose increased risk of cardiovascular disease. Few studies have prospectively investigated cardiovascular events related to depression in older women. We describe prevalence, cardiovascular correlates, and relationship to subsequent cardiovascular events of depressive symptoms among generally healthy postmenopausal women.

Methods: The Women's Health Initiative Observational Study followed up 93 676 women for an average of 4.1 years. Depression was measured at baseline with a short form of the Center for Epidemiological Studies Depression Scale. Risks of cardiovascular disease (CVD) events were estimated from Cox proportional hazards models adjusting for multiple demographic, clinical, and risk factor covariates.

Results: Current depressive symptoms above the screening cutoff point were reported by 15.8% of women. Depression was significantly related to CVD risk and comorbidity (odds ratios ranging from 1.12 for hypertension to 1.60 for history of stroke or angina). Among women with no history of CVD, depression was an independent predictor of CVD death (relative risk, 1.50) and all-cause mortality (relative risk, 1.32) after adjustment for age, race, education, income, diabetes, hypertension, smoking, high cholesterol level requiring medication, body mass index, and physical activity. Taking antidepressant medications did not alter the depression-associated risks associated.

Conclusions: A large proportion of older women report levels of depressive symptoms that are significantly related to increased risk of CVD death and all-cause mortality, even after controlling for established CVD risk factors. Whether early recognition and treatment of subclinical depression will lower CVD risk remains to be determined in clinical trials.

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DEPRESSIVE SYMPTOMS, including those that do not in themselves constitute clinical depression, have been reported to be independent risk factors for cardiovascular mortality in many studies,[1-5] although not all,[6] and an increase in such symptoms may be an early warning sign of impending events.[7] The association between emerging depressive symptoms over time and cardiovascular events raises several interpretive possibilities: increasing depression may be the cause of the cardiovascular event; or an impending cardiovascular event may be responsible for subclinical symptoms, one manifestation of which is increasing depression; or some third unknown set of factors might account for both the event and the depressive symptoms. It is not known whether depression acts through its effects on cardiovascular risk factors or whether it is independently related to cardiovascular events.

This article describes prevalence, cardiovascular correlates, and relationship to subsequent cardiovascular events of depression measured on a screening instrument, among a multiethnic cohort of nearly 100 000 generally healthy postmenopausal women enrolled in the 40 centers of the Women's Health Initiative Observational Study (WHI-OS).[8] The WHI-OS is a long-term prospective cohort study to identify and assess the impact of biological, lifestyle, biochemical, and genetic factors for the risk of heart disease, cancer, osteoporosis, and other major health problems of older women. The findings reported herein pertain to women enrolled throughout the period from September 1993 through December 1998 and represent the largest cohort of older women providing data on cardiovascular correlates of depression and on a prospective investigation of depression as an independent risk factor for subsequent cardiovascular events.

METHODS

STUDY POPULATION

The WHI-OS cohort of 93 676 participants is multiethnic, with 0.5% American Indian–Alaskan Native, 8.2% African American, 2.9% Asian–Pacific Islander, 3.9% Hispanic, 83.3% white, and 1.4% unknown. Postmenopausal women aged 50 to 79 years who gave written informed consent were recruited into the WHI at 40 clinical centers in the United States, mostly through mass mailings to age-eligible women from large mailing lists. Details of the WHI design are reported elsewhere.[8] Exclusions were participation in other randomized trials, predicted survival of less than 3 years, alcoholism, drug dependency, diagnosed mental illness, dementia, or other conditions making women unable to participate in the study.

DEFINITIONS OF VARIABLES

Depressive symptoms in the past week were assessed with a scale that used 6 items from the 20-item Center for Epidemiological Studies Depression Scale (CES-D),[8-11] which is commonly used in epidemiologic studies,[12] and 2 items from the Diagnostic Interview Schedule (DIS).[13] For the CES-D, participants are asked how often they have felt each of the feelings listed below during the past week. Each item is scored as 0 (rarely or none of the time [<1 day]), 1 (some or a little of the time [1-2 days]), 2 (occasionally or a moderate amount of the time [3-4 days]), or 3 (most or all of the time [5-7 days]).

1. You felt depressed.
2. Your sleep was restless.
3. You enjoyed life (reversed scoring).
4. You had crying spells.
5. You felt sad.
6. You felt that people disliked you.

The DIS items were as follows:

1. In the past year, have you had 2 weeks or more during which you felt sad, blue, or depressed or lost pleasure in things that you usually cared about or enjoyed? (0, no; 1, yes)
2. Have you had 2 years or more in your life when you felt depressed or sad most days, even if you felt okay sometimes? (0, no; 1, yes) If yes, have you felt depressed or sad much of the time in the past year? (0, no; 1, yes)

These items were administered at baseline as part of an extensive behavioral and psychosocial questionnaire to all women enrolling in the WHI and were originally selected for this questionnaire because they are used in a logistic regression equation[14] for a depression-screening algorithm developed by Burnam and colleagues.[14] In this report, we have chosen to use only the 6 CES-D items as an index of current depression, rather than the algorithm, because the CES-D is commonly used in epidemiologic studies and will make our results comparable with those of other surveys. The 2 DIS items, which ask about feelings of sadness or depression for 2 or more weeks in the past year and feelings of sadness on most days for 2 or more years, are stem questions for major depression and for dysthymia, respectively.[13] We combined the 2 DIS items separately, so that a person responding "yes" to both items was classified as having "history of depression."

The 6 CES-D items have been found to correlate with the full 20-item scale with $r = 0.88$ (unpublished data, available from S.W.-S., 2000), in a population similar to that of the WHI, consisting of 2682 women aged 60 to 79 years who were participants in the Systolic Hypertension in the Elderly Program (SHEP).[15] The distribution of CES-D scores is skewed, and a common cutoff point of the full 20-item CES-D in screening for depression is a score of 16 or greater[7,9,10] of a possible maximum score of 60. In the short-form CES-D used here, we use a cutoff point of 5 (of a possible 18), which corresponds to the cutoff point of 16 on the full scale. In the SHEP sample, there was 95% agreement in classification as depressed with the cutoff point of 16 or greater on the 20-item scale and with the cutoff point of 5 or greater on the 6-item short scale. This is a screening instrument, which may also reflect anxiety or psychological distress, and if used clinically, persons with CES-D above the cutoff point would generally be referred for further psychiatric evaluation. Thus, the screening result does not in itself constitute clinical depression. For notational convenience, in this report we use the term *current depression* for women who have a score of 5 or more on the short form of the CES-D.

Treatment for depression was determined from medications. Women were asked to bring in their original pill bottles to the baseline visit, and the label information was entered into the pharmacy database (Master Drug Data Base; Medi-Span, Indianapolis, Ind). Antidepressants included treatment with monoamine oxidase inhibitors, modified cyclics, selective serotonin reuptake inhibitors (SSRIs), tricyclic agents, and any other miscellaneous medications classified as antidepressants.

Hypertensive subjects were defined as those who had elevated blood pressure at the baseline clinic visit (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) and/or self-reported that they were taking medications for hypertension. Treated hypertensive subjects were those among the hypertensive individuals who reported that they were taking pills for high blood pressure. All women were asked to bring all the prescription medications and over-the-counter drugs and supplements they were taking to the baseline visit. Self-report of taking antihypertensive medication was confirmed for 85% of women by the medications they brought in that fell into the antihypertensive drug categories.

History of various CVD events was obtained by self-report on baseline questionnaires. Height, weight, and blood pressure were measured at the baseline visit. High cholesterol level was defined as self-report of having a high cholesterol level requiring pills; we did not have blood measures of cholesterol in the entire WHI-OS cohort. Overweight was defined as body mass index (BMI) greater than 27.3 (measured as weight in kilograms divided by the square of height in meters). Physical activity was assessed by questions ascertaining episodes per week of moderate or strenuous activity (defined by a metabolic equivalent score of at least 4.0 as indicated by Ainsworth and colleagues[16]) of at least 20 minutes' duration. One metabolic equivalent is the amount of energy expended sitting quietly at rest, adjusted to body weight, equal to 1 kcal/kg per hour. Women reporting some recreational activity but of shorter duration and/or lesser intensity were classified as having "some activity."

END POINT ASCERTAINMENT

Potential outcomes were identified from annual Medical History Update questionnaires, or participant or third-party reports directly to clinic staff in the intervals between questionnaires, followed by obtaining medical record information. Participant fatalities were identified through communication with proxy respondents and also through the National Death Index searches. Vital status was available for 98.2% of respondents as of February 28, 2001. Packets of complete information were prepared and presented to physician adjudicators at the clinical sites who made the decision on cause of event. End points were the first occurrence of the following: congestive heart failure; coronary heart disease (CHD), defined as fatal or nonfatal myocardial infarction (MI); coronary artery disease,

Table 1. Depressed Mood by Demographic Characteristics

	No. of Subjects	Currently Depressed at Baseline		History of Depression	
		%	95% CI	%	95% CI
All subjects	93 676	15.8	15.6-16.0	12.3	12.1-12.5
Age group at screening, y					
50-59	29 705	18.1	17.7-18.5	15.7	15.3-16.1
60-69	41 197	14.8	14.5-15.1	11.4	11.1-11.7
70-79	22 774	14.5	14.0-15.0	9.3	8.9-9.7
Ethnicity					
American Indian–Alaskan Native	422	25.8	21.6-30.0	21.1	17.2-25.0
Asian–Pacific Islander	2671	10.8	9.6-12.0	8.3	7.3-9.3
Black	7639	19.0	18.1-19.9	14.5	13.7-15.3
Hispanic	3623	26.9	25.5-28.3	19.9	18.6-21.2
White, not of Hispanic origin	78 013	15.0	14.7-15.3	11.7	11.5-11.9
Unknown	1308	18.4	16.3-20.5	15.7	13.7-17.7
Education					
0-8 y	1560	29.9	27.6-32.2	23.1	21.0-25.2
Some high school	3288	25.1	23.6-26.6	19.7	18.3-21.1
High school diploma/GED	15 121	17.8	17.2-18.4	13.4	12.9-13.9
School after high school	33 933	16.7	16.3-17.1	13.0	12.6-13.4
College degree or higher	39 002	12.7	12.4-13.0	10.1	9.8-10.4
Family income, $					
<10 000	3912	29.2	27.8-30.6	25.2	23.8-26.6
10 000-19 999	10 100	22.0	21.2-22.8	17.6	16.9-18.3
20 000-34 999	20 226	17.0	16.5-17.5	12.7	12.2-13.2
35 000-49 999	17 429	14.6	14.1-15.1	11.2	10.7-11.7
50 000-74 999	17 486	12.9	12.4-13.4	10.6	10.1-11.1
≥75 000	17 608	11.3	10.8-11.8	8.3	7.9-8.7
Marital status					
Never married	4390	15.7	14.6-16.8	12.8	11.8-13.8
Divorced/separated	14 727	20.6	19.9-21.3	18.3	17.7-18.9
Widowed	16 290	18.1	17.5-18.7	14.4	13.9-14.9
Presently married or living as married	57 804	13.8	13.5-14.1	10.0	9.8-10.2

Abbreviations: CI, confidence interval; GED, general equivalency diploma.

defined as MI or coronary death, angina, coronary artery bypass grafting, or angioplasty; stroke, fatal or nonfatal; and CVD death, defined as death caused by definite or possible CHD, cerebrovascular disease, pulmonary embolism, or other or unknown type of CVD. Follow-up was on average 4.1 years (SD, 1.2 years; interquartile range, 3.0-4.9 years; maximum follow-up time, 6.9 years).

STATISTICAL ANALYSIS

Prevalence of depression and 95% confidence intervals (CIs) are presented for demographic subgroups. Logistic regression models were run with baseline depression as the dependent variable, to determine odds ratios (ORs) and 95% CIs for lifestyle and cardiovascular risk factors, and for history of cardiovascular conditions. Kaplan-Meier survival curves were obtained for stroke, cardiovascular death, and all-cause mortality.

To determine the effect of depression on subsequent cardiovascular events, Cox proportional hazards models were run to obtain relative risks (RRs) of CVD end points associated with depression, controlling for age, race, education, income. Additional models were run, further controlling for variables significantly related to depression and known to be related to CVD outcomes: diabetes, hypertension, smoking, high cholesterol level requiring medications, BMI, physical activity, and hormone use. Some models also included use of antidepressant medications. We did not include in these multivariate analyses variables that are presumed from past experience to be collinear or intermediate in the pathway relating depression to CVD events, such as self-reported health, disability, or alcohol use (which has a U-shaped relationship with some cardiovascular events), as control for such variables may distort the effect estimates of depression. The objective of these analyses was to see whether effects of depression on CVD end points remained after accounting for the established risk factors.

Models were run separately for those with and without history of CVD. Depression in the Cox models was defined as current or history of depression. The reference group was characterized by not being currently above the cutoff score of 5 or more on the CES-D 6-item screen and not having a history of depression at baseline as measured by the 2 DIS items. For events that were significantly related to depression in these analyses, models were also run excluding events in the first 6 months after baseline measure of depression. In some analyses, where specified, depression was defined as current or history of depression or taking antidepressant medication.

RESULTS

PREVALENCE OF DEPRESSED MOOD

Overall, 15.8% (95% CI, 15.6%-16.0%) of women reported current depressed mood at baseline (**Table 1**) and 12.3% (95% CI, 12.1-12.5) reported history of depressed mood.

Table 2. Cardiovascular Risk Factors and Adjusted Odds Ratios of Current Depression

	No. of Subjects	OR* (95% CI)
Demographic Variables		
Education†		
0-8 y	1560	1.00
Some high school	3288	1.01 (0.87-1.17)
High school diploma/GED	15 121	0.73 (0.64-0.84)
School after high school	33 933	0.76 (0.66-0.86)
College degree or higher	39 002	0.65 (0.57-0.75)
Family income, $‡		
<10 000	3912	1.00
10 000-19 999	10 100	0.72 (0.67-0.78)
20 000-34 999	20 226	0.51 (0.47-0.55)
35 000-49 999	17 429	0.42 (0.39-0.45)
50 000-74 999	17 486	0.36 (0.33-0.39)
≥75 000	17 608	0.29 (0.27-0.32)
Lifestyle Variables		
Smoking		
Never smoked	47 023	1.00
Past smoker	39 514	1.08 (1.04-1.13)
Current Smoker	5791	1.29 (1.20-1.39)
Overweight (BMI >27.3)		
No	54 485	1.00
Yes	38 083	1.26 (1.22-1.31)
Weight/smoking status		
Nonoverweight/nonsmoker	27 523	1.00
Past smoker	22 576	1.09 (1.03-1.15)
Current smoker	3623	1.42 (1.30-1.57)
Overweight nonsmoker	18 961	1.30 (1.23-1.38)
Past smoker	16 459	1.39 (1.31-1.47)
Current smoker	2093	1.56 (1.39-1.75)
Alcohol consumption		
Nondrinker	10 477	1.00
Past drinker	17 555	1.35 (1.26-1.45)
<1 drink/wk	29 461	1.17 (1.10-1.26)
1-6 drinks/wk	23 842	1.09 (1.02-1.18)
≥7 drinks/wk	117	1.04 (0.96-1.13)
Exercise (episodes/wk of moderate or strenuous activity ≥20 min)		
None	12 637	1.00
Some	35 648	0.78 (0.74-0.82)
2-4	17 093	0.67 (0.62-0.71)
>4	27 251	0.56 (0.53-0.59)
Hormone use		
Unopposed estrogen		
Never	58 953	1.00
Past	11 421	1.32 (1.24-1.41)
Current	23 227	1.25 (1.18-1.32)
Estrogen + progesterone		
Never	67 225	1.00
Past	8207	1.25 (1.16-1.35)
Current	18 202	1.07 (1.00-1.14)
Cardiovascular Risk Factors		
Cholesterol requiring pills		
No	77 835	1.00
Yes	13 774	1.17 (1.11-1.23)
Hypertension status		
Normotensive	52 255	1.00
Hypertensive	36 183	1.12 (1.07-1.116)
Treatment of hypertension		
Untreated	12 198	1.00
Treated	23 464	1.15 (1.07-1.22)
Diabetes, treated (oral or injection)		
No	89 654	1.00
Yes	3902	1.50 (1.38-1.63)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; GED, general equivalency diploma; OR, odds ratio.

*Adjusted for age, race, education, and income (unless otherwise noted).

†Adjusted for age, race, and income.

‡Adjusted for age, race, and education.

Rates of depression were highest among Hispanic and American Indian–Alaskan Native women and lowest among Asian–Pacific Islanders. There was an inverse dose-response relationship of depression to age, education (ranging from 12.7% for current depression of those with a college degree or higher to 29.9% of those with less than an eighth grade education), and income. History of depression followed the same pattern. The results that follow pertain to baseline current depressed mood unless otherwise noted.

DEPRESSION AND CARDIOVASCULAR RISK FACTORS

Lifestyle cardiovascular risk and protective factors were all related to current depression (**Table 2**) at baseline after adjustment for age, race, education, and income. Both being overweight and smoking were significantly related to depression. Compared with nonoverweight nonsmokers, those both overweight and currently smoking had 1.56 times the risk of current depression (95% CI, 1.39-1.75).

There was an inverse dose-response relationship of depression and exercise level, which, compared with nonexercisers, ranged from only 0.56 the risk among those who had 4 or more episodes of moderate or strenuous activity of at least 20 minutes' duration, to 0.67 for those with 2 to 4 such episodes and 0.78 for those who reported some activity. The CIs did not overlap. The same relationships held true for history of depression. All of these ORs for cardiovascular lifestyle risk factors remained substantially unchanged when further adjusted for diabetes, arthritis, and history of CVD. Nevertheless, self-reported fair or poor health, compared with excellent or very good health, was strongly associated with depression (OR, 4.73) (data not shown).

Compared with no medication use, current unopposed estrogen use was associated with a greater risk of current depression (OR, 1.25; 95% CI, 1.18-1.32) as was use of estrogen plus progesterone (OR, 1.07; 95% CI, 1.00-1.74). Since unopposed estrogen is most often used in women who have had a hysterectomy, the higher risk of depression among these women may be partly associated with the hysterectomy. Therefore, we compared logistic regressions for women with a uterus and without a uterus separately (data not displayed). The OR for depression in women using unopposed estrogen who had a uterus was 1.31 (95% CI, 1.11-1.54), and for those without a uterus it was 1.17 (95% CI, 1.07-1.28).

Comorbid cardiovascular risk factors, adjusted for age, race, education, and income, were all significantly related to reported depression, ranging from OR of 1.12 for hypertensive subjects compared with normotensive individuals to an OR of 1.50 for individuals with confirmed diabetes (ie, those being treated for diabetes with pills or shots) compared with nondiabetic subjects. History of various forms of CVD was strongly associated with risk of depression (**Table 3**). Women with a history of angina were 57% more likely to report current depression than those without a history of CVD. Higher ORs for depression were also found for those with a history of MI (OR, 1.45), stroke (OR, 1.60), atrial fibrillation (OR,

1.48), cardiac catheterization, angioplasty, or coronary bypass surgery (ORs, 1.41, 1.57, and 1.28, respectively), or congestive heart failure (OR, 1.63). To determine whether the increased risk of depression among those with CVD is specific to CVD conditions, we also looked at cancer and at stomach or duodenal ulcer and depression (not displayed). The OR for current depression among those with a history of cancer vs no cancer was 1.14 (95% CI, 1.08-1.21). The OR for current depression and history of stomach or duodenal ulcer was 1.52 (95% CI, 1.42-1.62). This suggests that history of various morbidities may lead to reported current depression.

TREATMENT OF DEPRESSION AND CRUDE EVENT RATES

Of the entire cohort, 7.7% (95% CI, 7.5%-7.8%) were taking antidepressive medications. Of the 14 764 women who were above the cutoff point for depression on the 6-item CES-D screen, 14.7% (95% CI, 14.2%-15.3%) were taking these drugs compared with 6.3% of those who did not meet the cutoff point for depression on the CES-D screen. Of the 7043 women taking antidepressant medications, 49.9% were taking SSRIs (data not displayed). **Table 4** shows the crude event rates for those with current depression or a history of depression and for those not depressed. For each event except cancer, the unadjusted rates were higher for those depressed than for those not depressed.

The **Figure** displays Kaplan-Meier survival curves for those depressed and not depressed for the entire cohort. For stroke the curves begin to diverge after about 1 year, for cardiovascular death after about 6 months, and for all-cause mortality before 6 months. The curves, particularly of cardiovascular deaths, become more separate over time, indicating that the effect of depression is not just immediately after the baseline measurement.

PROSPECTIVE RISK OF CARDIOVASCULAR END POINTS IN RELATION TO BASELINE DEPRESSION

To determine whether depression is an independent predictor of cardiovascular events, we ran Cox proportional hazards models to obtain RRs of these events for those who reported depressive symptoms at baseline (score ≥5 on CES-D items or reporting history of depressed mood). The reference group consisted of those neither depressed at baseline nor reporting history of depressed mood on the screening instrument. Because the interaction between history of CVD and depression was significant in models on coronary disease, and because a history of CVD may cause depression, we considered those without and with history of CVD separately (n=73 098 and 18 572, respectively) (**Table 5**).

Among women with no history of CVD, baseline depression adjusted for age and race was associated with a 58% higher risk of CVD death (RR, 1.58; 95% CI, 1.19-2.10). The association remained significant after additional adjustment for education and income (RR, 1.52; 95% CI, 1.13-2.05). Further adjustment for diabetes, hypertension, smoking, and high cholesterol level requiring medications, BMI, physical activity, and hormone use did not affect the RR (RR, 1.50; 95% CI, 1.10-2.03), indicating that the traditional risk factors do not account for the association of depression with cardiovascular death among those with no history of CVD at baseline. Censoring events that occurred in the first 6 months after the baseline measure of depression also did not affect the risk (RR, 1.59; 95% CI, 1.12-2.10). In models additionally adjusting for being treated for depression, the RR was essentially unchanged (RR, 1.40; 95% CI, 1.03-1.91; not displayed). For comparison purposes, in these models the adjusted RR of CVD death for hypertension was 2.19 (95% CI, 1.64-2.93); for diabetes, 2.54 (95% CI, 1.60-4.03); and for current smoking, 3.66 (95% CI, 2.39-5.62); adjusted RRs were not significant for BMI, income, education, race, or ethnicity (data not shown).

Depression, controlling for the multiple covariates, was also independently associated with all-cause mortality (RR, 1.32; 95% CI, 1.16-1.52). In models where the definition of depression also included those taking antidepressant medications, even if their current depressive symptoms were below the cutoff point, controlling for age, race, and the CVD risk factors, the risks were similar for cardiovascular death (RR, 1.62; 95% CI, 1.23-2.13) and for all-cause mortality (RR, 1.34; 95% CI, 1.18-1.51) (data not displayed).

The RR for coronary disease of baseline depression, adjusted for age and race, education income, diabetes, hypertension, smoking, high cholesterol level requiring medications, BMI, physical activity, and hormone use, was elevated but lower than for mortality outcomes (RR, 1.12; 95% CI, 0.97-1.29). Additionally adjusting for taking antidepressant medication did not affect this risk estimate (RR, 1.11). For these end points, the estab-

Table 3. History of CVD Events and Adjusted Odds Ratios for Current Depression

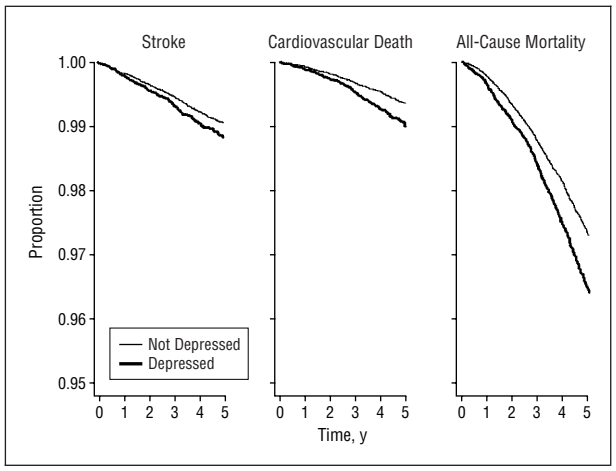
Variable	No. of Subjects	Baseline Current Depression OR*	(95% CI)
Angina ever			
No	88 863	1.00	
Yes	4372	1.57	(1.45-1.70)
Peripheral arterial disease ever			
No	91 740	1.00	
Yes	1467	1.60	(1.41-1.82)
Cardiovascular disease ever			
No	73 098	1.00	
Yes, any	18 572	1.41	(1.35-1.47)
Myocardial infarction	2306	1.45	(1.30-1.62)
Stroke	1415	1.60	(1.39-1.83)
Atrial fibrillation	4397	1.48	(1.36-1.60)
Cardiac catherterization	3837	1.41	(1.29-1.54)
Angioplasty of coronary arteries ever	1128	1.57	(1.34-1.82)
Coronary bypass surgery ever	881	1.28	(1.07-1.54)
Carotid endartarectomy/angioplasty	344	1.50	(1.13-1.99)
CHF	892	1.63	(1.38-1.93)
Aortic aneurysm	187	1.84	(1.28-2.65)
Cardiac arrest	348	1.19	(0.89-1.59)

Abbreviations: CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio.
*Adjusted for age, race, education, and income.

Table 4. Crude Event Rates

Events	Depressed (Current or History), %			Not Depressed (No Current and No History), %		
	All (N = 20 130)	Taking Antidepressant Medications (n = 3308)	Not Taking Antidepressant Medications (n = 16 822)	All (N = 71 546)	Taking Antidepressant Medications (n = 3735)	Not Taking Antidepressant Medications (n = 67 810)
Coronary artery disease	3.14	3.33	3.11	2.67	3.21	2.64
CHD	1.20	1.18	1.20	1.04	1.12	1.03
CHF	1.31	1.72	1.22	0.90	1.53	0.86
Stroke	0.97	0.91	0.99	0.79	1.12	0.77
Cancer	4.89	4.81	4.90	4.95	5.73	4.91
CVD death	0.79	1.00	0.75	0.52	0.75	0.51
All-cause death	2.87	3.42	2.76	2.18	3.11	2.13

Abbreviations: CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease.



Survival curves for those depressed and not depressed.

lished risk factors did not explain the elevated risks associated with depression.

For those who had a history of CVD, depression (controlling for age and race, education, and income) was independently and significantly associated with congestive heart failure, stroke, CVD death, and all-cause mortality; however, with adjustment for multiple risk factors, these RRs were reduced and depression remained significantly and independently related only to stroke (RR, 1.45; 95% CI, 1.11-1.90), even when events in the first 6 months were excluded (RR, 1.40; 95% CI, 1.05-1.87). For models that indicated a significant relationship of depression and the event after controlling for all the covariates noted above, interactions were examined between depression and the known risk factors; none was significant at the .01 level (which was selected to adjust for multiple testing). In contrast to CVD events, depression did not predict cancer incidence or death, either for those with or without a history of CVD, either with adjustment for age, race, education, and income or with full adjustment.

COMMENT

The WHI-OS of 93 676 women represents the largest cohort of postmenopausal women followed up prospectively who had baseline measures of depression and rigorously adjudicated outcome events. Our major findings are that (1) prevalence of depressive symptoms on a screening instrument is quite high, at 16%; (2) depression is significantly related to risk factors for CVD and history of cardiovascular morbidity; and (3) among those with no previous CVD, depression is an independent predictor of CVD and all-cause mortality. For those with a history of CVD, baseline depressive symptoms are significantly associated with stroke.

In the WHI, the 15.8% prevalence of reported depressive symptoms on a short form of the CES-D among women aged 50 to 79 years is within the range of 5% to 30% prevalence of possible depression, depending on age-sex-race groups, found in several other studies.[17-20] Hispanic and American Indian–Alaskan Native women had the highest rates of depression, while Asian–Pacific Islanders had the lowest rates, similar to other studies.[7,18,21]

We found that older women with established risk factors for CVD, such as smoking, obesity, low physical activity, hypertension, high cholesterol level, and diabetes, had an approximately 20% to 50% higher OR for current depression after adjustment for age, race, education, and income. Low income (adjusting for age, race, and education) and low educational level (adjusting for age, race, and income) were highly related to depression, but in our cohort they were not related to cardiovascular end points after adjustment for other risk factors. Similarly, women who have a history of various forms of CVD, such as angina, MI, revascularization, or stroke, also have higher odds of current depression. However, women with a history of cancer or ulcer also have higher risk of current depression, suggesting that several chronic disease conditions may lead to depressive symptoms. Compared with women who reported their health to be excellent, women who reported their health as being fair or poor were 4.8 times as likely to report depression (38% of them reported depression) as were those who reported their health as excellent (10%) (data not displayed).

It is important to note that persons with diagnosed mental illness were excluded from the WHI; therefore, the depression index used herein assesses subclinical depressive symptoms. We have found, in an average of 4.1 years of follow-up, that such symptoms are significant

Table 5. Baseline Depression* and Relative Risks of Subsequent Cardiovascular Events, Cancer, and All-Cause Mortality

End Point (No. of Events)†	RR (95% CI) Adjusted for: Age and Race	Age, Race, Education, and Income	Age, Race, Education, and Income + Risk Factors‡
No History of CVD (n = 73 098)			
Coronary artery disease (1254)	1.26 (1.10-1.44)	1.18 (1.02-1.36)	1.12 (0.97-1.29)
CHD (509)§	1.18 (0.95-1.46)	1.18 (0.95-1.48)	1.12 (0.89-1.41)
CHF (385)	1.42 (1.12-1.80)	1.27 (0.99-1.62)	1.16 (0.90-1.49)
Stroke (464)	1.09 (0.86-1.37)	1.10 (0.79-1.30)	1.01 (0.78-1.30)
Cardiovascular death (253)	1.58 (1.19-2.10)	1.52 (1.13-2.05)	1.50 (1.10-2.03)
		1.57‖ (1.15-2.13)	1.59‖ (1.12-2.10)
Cancer diagnosis (3471)	1.03 (0.95-1.12)	1.03 (0.95-1.13)	1.00 (0.92-1.10)
All-cause mortality (1350)	1.39 (1.23-1.58)	1.39 (1.22-1.59)	1.32 (1.16-1.52)
		1.36‖ (1.19-1.55)	1.29‖ (1.13-1.49)
History of CVD (n = 18 572)			
Coronary artery disease (1290)	1.08 (0.95-1.23)	1.00 (0.88-1.15)	0.92 (0.80-1.05)
CHD (469)	1.16 (0.94-1.42)	1.07 (0.87-1.33)	0.94 (0.75-1.18)
CHF (530)	1.40 (1.17-1.69)	1.25 (1.03-1.52)	1.14 (0.93-1.40)
Stroke (287)§	1.55 (1.21-1.98)	1.53 (1.18-1.99)	1.45 (1.11-1.90)
		1.51‖ (1.14-1.99)	1.40‖ (1.05-1.87)
Cardiovascular death (282)	1.49 (1.16-1.92)	1.37 (1.04-1.79)	1.22 (0.92-1.61)
Cancer (1008)	1.02 (0.88-1.17)	1.02 (0.88-1.18)	0.99 (0.85-1.16)
All-cause mortality (784)	1.32 (1.13-1.54)	1.20 (1.02-1.42)	1.10 (0.93-1.31)

Abbreviations: CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.

*Depression was defined as current depressed mood or history of depression. Reference group had no current or history of depression.

†Coronary disease was defined as myocardial infarction or coronary death, angina, coronary artey bypass grafting, or angioplasty; CHD, as myocardial infarction or coronary death; stroke, as fatal or nonfatal stroke; and cardiovascular death, as definite or possible CHD, cerebrovascular disease, pulmonary embolism, and other or unknown type of cardiovascular disease.

‡Body mass index, cholesterol, diabetes, smoking, hormone therapy, physical activity, and hypertension status.

§$P<.001$ for effect of antidepressants.

‖Events occurring in the first 6 months were censored.

independent predictors of CVD events. Because CVD may be a cause of depression, and because several studies have found that post-MI depression carries a poorer prognosis than that for patients after MI who are not depressed,[22] we performed separate analyses for women who had no history of CVD. It should be noted, however, that we cannot completely rule out the possibility that even among those with no history of CVD, undetected CVD may have caused depression.

Other smaller studies have reported results similar to ours.[23] In the Study of Osteoporotic Fractures of 7518 white women aged 67 years or older with a 6-year follow-up, the investigators found an 80% higher risk associated with depression for cardiovascular deaths after adjustment for multiple covariates, but found no association with deaths from cancer.[23] In our study of 93 726 women, we found a 50% increased risk of CVD deaths associated with depression among women with no previous CVD, and we also found no association with cancer incidence or deaths, although a Finnish study[24] did find a higher risk of lung cancer associated with depression. The Glostrup study from Denmark[25] followed up 409 men and 321 women for 27 years and found that a 2-SD difference in depression scores measured at baseline was associated with a 71% increase in MI and a 59% increase in deaths from all causes, with no difference in effect sizes for men and women. The long-lasting nature of this effect suggested to the authors that this risk factor represents a chronic psychological characteristic.

Four large prospective studies that used the CES-D, which was the measure of depression used in the WHI, looked at the association of heart disease and depression: the National Health and Nutrition Examination Survey,[26] the Cardiovascular Health Study,[27] the Established Populations for Epidemiologic Studies of the Elderly,[28] and the Systolic Hypertension in the Elderly Program.[29]

In the National Health and Nutrition Examination Survey I, 5007 women and 2886 men recruited from 1982 through 1984 were studied for CHD through 1992 and were free of CHD at baseline.[26] The adjusted RRs, from Cox proportional hazards models, for all nonfatal CHD events were similar in women (RR, 1.73; 95% CI, 1.11-2.68) and in men (RR, 1.79; 95% CI, 1.14-2.56). However, for fatal CHD events it was 0.74 (0.40-1.48) and 2.34 (1.54-3.56), respectively, for women and men.

In the Cardiovascular Health Study,[27] 5888 men and women older than 65 years were recruited and followed up for 6 years, of whom 4493 were free of known heart disease at baseline. The investigators found that for every 5-units-higher mean depression score on the CES-D, after adjustment for multiple covariates, the hazard ratios for CHD and all-cause mortality were 1.15 and 1.16, respectively ($P=.006$). There was no interaction with sex. The Systolic Hypertension in the Elderly Program, a clinical trial of antihypertensive therapy in 4367 generally healthy men and women 60 years or older, with an average follow-up of 4.5 years, found that a 5-point in-

crease in CES-D during the trial significantly increased risk of stroke or MI (RR, 1.18; 95% CI, 1.08-1.30), after excluding those with events during the first 6 months and controlling for multiple covariates. Increase in CES-D score was an independent predictor of death, stroke, or MI in both placebo and drug-treated groups.[7]

However, data from the Established Populations for Epidemiologic Studies of the Elderly longitudinal study[28] of 4162 men and women 65 years or older at baseline found that after adjustment for multiple covariates, CES-D depression was not associated with mortality in either sex, although it was significantly and directly associated in analyses without control for other variables, but subthreshold depression was negatively related to mortality in women but not men. It is difficult to compare these results with ours because the definition of subthreshold depression used in that report may not be equivalent to what we label as subclinical depression. The subthreshold depression was based on number rather than severity of symptoms, and we used a different cutoff point. It is also possible that differences in control variables used in the 2 studies may have resulted in different effect estimates. In contrast, another 7-year prospective study of 2558 individuals 65 years or older, reported by Unutzer and colleagues,[30] showed that mild to moderate baseline depression did not have an effect on mortality, but more severe depressive symptoms were associated with significant increases in mortality. Thus, these studies show somewhat inconsistent results, with the National Health and Nutrition Examination Survey indicating no effect of CES-D score on subsequent fatal CHD events in women and a large effect in men, the Cardiovascular Health Study showing modest effects on CVD events in women, and Established Populations for Epidemiologic Studies of the Elderly showing no effect of higher depression scores on mortality, but an inverse effect for subthreshold depression in women.

In our study, where the follow-up was for an average of 4.1 years and which is substantially larger than other prospective studies to date (N=93676), the adjusted RR for all-cause mortality was 1.32 and for CVD deaths was 1.50 among those with no history of CVD, substantially higher than in the Cardiovascular Health Study. While there are somewhat inconsistent results across studies, partly due to different cutoff points in depression measures and possibly to differences in population characteristics, the weight of the overall evidence seems to show that subclinical depression increases risk of subsequent morbidity and mortality, and our study supports that conclusion.

Given the mounting evidence that depression is an independent risk factor for cardiovascular events in those both with and without a history of CVD, there is growing interest in whether treatment of depression may lower risk. There is also growing interest in identifying depression in a primary care setting.[31] The suggestion that SSRIs may confer a protective effect against MI comes from a report by Sauer and colleagues[32] of a case-control study in 30- to 65-year-old smokers of 653 cases of first MI and 2990 controls. The investigators found an OR of 0.35 among current SSRI users compared with nonusers after adjustment for multiple covariates. The Enhancing

Recovery in Coronary Heart Disease Study, whose objective was to determine the effect of treatment for depression and social support with cognitive behavioral therapy and SSRIs[33] on subsequent morbidity and mortality in patients after MI (N=2481), has reported no effect on event-free survival. There have been no clinical trials addressing this issue in women with no history of heart disease. In our prospective analyses, controlling for use of antidepressants did not alter the RRs of subsequent events associated with baseline depression. It is possible that women who report depressive symptoms are less adherent to medications for other cardiovascular risk factors, which then puts them at greater risk of CVD events. We controlled for baseline risk factor status and lifestyle variables that affected CVD risk in our analyses, but had no measures of adherence to medications.

Various biological mechanisms have been suggested to link depression and depressive symptoms to CHD. Two main avenues are through the effects of depression on lipid metabolism and through altered sympathetic arousal in depressed patients.[34,35] Mechanisms of increased risk of death in patients with depression after MI may include arrhythmia.[36,37] Alteration in the ratio between sympathetic and parasympathetic tone may make patients more susceptible to arrhythmia by lowering the threshold for ventricular fibrillation.[38,39] Increased platelet aggregation may also be a contributory factor.[40] Another mechanism that is gaining attention is an inflammatory process. High C-reactive protein level, which is a marker of inflammation, has been found to be predictive of CVD[41] and possibly may be related to depression. A study from Germany by Rothermundt and colleagues[42] failed to support the hypothesis that major depression is associated with global inflammation as measured by C-reactive protein, although patients with one type of depression (nonmelancholic) did show higher levels of C-reactive protein than healthy controls. This is an area that merits further investigation.

In conclusion, we have found, in the largest multiethnic volunteer cohort of older women to date, that subclinical depression is a prevalent condition that is related to cardiovascular risk factors and cardiovascular comorbidity. It is an independent risk factor for subsequent cardiovascular death, particularly in those who have no history of CVD, at a lower level than diabetes or hypertension and at a higher level than BMI, income, education, race, or ethnicity. Whether treatment with antidepressants of those with no history of CVD will lower the risks remains to be determined in a randomized clinical trial of this question.

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Correction

Error in "Results" Section. In the Original Investigation by Fick et al titled "Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults," published in the December 8/22 issue of the ARCHIVES (2003; 163:2716-2724), an error occurred in the "Results" section on page 2720. The second full sentence in the left column should have read "Reserpine was changed to be avoided only at doses greater than 0.25 mg, and disopyramide phosphate avoidance now only refers to the non–extended release formulation." This correction was made previously to online versions of this article.