Depressive symptoms and longitudinal changes in cognition: Women's Health Initiative Study of Cognitive Aging

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Abstract

Elevated Depressive symptoms (DS) are associated with incident mild cognitive impairment and probable dementia in postmenopausal women. We examined the association of elevated DS with domain-specific cognitive changes, and the moderating role of cardiovascular risk factor (CVRF) severity and cardiovascular disease (CVD). 2221 elderly women who participated in the Women's Health Initiative Study of Cognitive Aging were separated into those with (N = 204) and without (N = 2017) elevated DS. DS and multi-domain cognitive outcomes were measured annually for an average follow-up of 5.04 years. Women with elevated DS showed baseline multi-domain cognitive deficits, but longitudinal declines in global cognition only. Persistent DS was related to greater global cognition, and verbal knowledge and fluency, and memory declines. Significant DS-CVD interactions were observed cross-sectionally (but not longitudinally) for figural memory and fine motor speed. Future studies should investigate the role of nonvascular mechanisms linking DS and cognitive decline.

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INTRODUCTION

Clinically significant depression occurs in 15% of the elderly and a significant majority of these individuals has milder depressive symptoms (DS) that fall short of the criteria for syndromal late-life depression (LLD). The number of elderly women suffering from elevated DS is expected to increase exponentially in the coming decades. Furthermore, the public heath consequences of incident cognitive decline and Alzheimer's Disease (AD) are significantly greater for women than men largely due to women's longer life expectancy. While LLD has been associated with an increased risk of incident cognitive decline and Alzheimer's disease (AD), the effects of milder DS on future cognitive health is less clear. In the Women's Health Initiative Memory Study (WHIMS), elevated DS was associated with an increased risk of mild cognitive impairment (MCI) and probable dementia in those 65 years of age and older. Late-life DS are also associated with longitudinal declines in psychomotor speed and executive functions in mixed gender studies, although the effects on episodic memory and nonmemory cognitive measures over time in elderly women remains elusive. Moreover, the differential effects of fluctuating and persistently elevated DS on domain-specific cognitive changes are poorly understood.

Of the prospective studies that have examined the longitudinal associations of late-life DS with domain-specific cognitive functions, most did not include a control group, and/or measured cognitive functions at limited timepoints. Moreover, only a handful of investigations have examined the effects of persistent DS on the longitudinal cognitive performance, and the findings vary. While persistent DS was associated with only declines in information processing speed in one study, symptom chronicity in patients with coronary heart disease was related to multi-domain cognitive decline in another study. Additional investigations of the complex relationships between DS and longitudinal cognitive changes, and the mechanisms that explain their associations in postmenopausal women are critically needed.

Vascular etiologies are hypothesized to play a critical role in linking depression and cognitive decline. Late-life DS are often co-morbid with cardiovascular risk factors (CVRFs) and cardiovascular and cerebrovascular disease. The co-existence of CVRFs and cardiovascular disease (CVD) with late-life DS is related to worse treatment outcomes and greater cognitive decline. Also, there is a bi-directional relationship between LLD and CVRF and vascular disease, and these observations support the 'vascular depression' hypothesis. While emerging evidence indicates that worsening subclinical cerebrovascular disease in depressed elderly may be associated with future development of dementia, primarily of non-Alzheimer's type, others have not found an influence of vascular disease on late-life DS-cognitive impairment relationships. CVRFs and CVD are also independently associated with an increased risk of cognitive decline and incident dementia. The

moderating role of CVRF severity and CVD on the relationship of DS with longitudinal changes in memory and non-memory measures in elderly women remains poorly understood.

The data from a large, well-characterized cohort of postmenopausal women who participated in the Women's Health Initiative Study of Cognitive Aging (WHISCA) were utilized here (1) to determine the relationship of DS and domain-specific cognitive changes, and (2) to investigate the moderating effects of CVRF and CVD on various cognitive measures in those with DS, over a seven-year follow-up period.

METHODS

Participants

WHISCA, an ancillary study to the Women's Health Initiative (WHI) randomized, placebo-controlled clinical trial of hormone therapy (HT) regimens based on conjugated equine estrogens, enrolled 2304 postmenopausal women between ages 65 and 79 from 14 of 40 WHI clinical sites. WHISCA assessments began an average of 3 years after the WHI randomization to treatment. The study design, participant eligibility criteria, recruitment procedures, and principal findings of WHISCA have been previously published. The National Institute of Health (NIH) and the institutional review boards at the participating clinical centers approved WHISCA study protocols. All participants provided informed consent. The WHISCA participants who had completed at least the initial cognitive assessment and contributed complete data on baseline characteristics were included in this analysis (**Table 1**). In addition, women who were free of MCI and probable dementia at WHISCA enrollment were included in this study. After excluding 83 women who did not meet the above criteria, the final *cross-sectional* sample was comprised of a total of 2221 participants. Among the 2221 participants, 2123 women finished at least one follow-up assessment for the longitudinal analysis focused on change in cognitive performance from baseline.

Depressive symptom assessments

DS were assessed annually over up to 7 years using the 15-item Geriatric Depression Scale (GDS). A score of 5 or above at WHISCA initial assessment was considered as elevated DS. A cutoff point of 5 have been previously demonstrated as having excellent validity for detecting major depression in the elderly. Additionally, women were classified based on the presence or absence of elevated DS at WHISCA year 1 follow-up: Participants were considered to have persistently elevated DS if they scored positive (i.e., > 5 on GDS) at both WHISCA first (i.e., enrollment) and second (i.e., Year 1) visits; fluctuating DS if they scored positive at only one visit, and no DS if they scored negative (i.e., <5 on GDS) at both visits. This analysis cohort consisted of 2046 women who returned one year later for follow-up assessment.

Cardiovascular risk factor score and cardiovascular disease

We calculated the CVRF score closest to WHISCA baseline using the model described previously. Briefly, age, systolic blood pressure (BP), use of antihypertensive treatment,

current smoking history, history of diabetes mellitus, and body mass index (BMI) were included in this non-laboratory based CVRF model which previously has been shown to predict CV events as accurately as risk factor indices based on laboratory-based values. Women with a history of CVD at WHISCA baseline assessment and those having missing variables required for the CVRF score calculation were excluded from this analysis. Therefore, the final cohort for this analysis was comprised of 1820 women. The CVRF score ranged from 0.03 to 0.80.

History of CVD was defined as either a self-report of myocardial infarction, coronary bypass surgery, angioplasty, congestive heart failure, angina, carotid endarterectomy/angioplasty, cardiac catheterization, aortic aneurysm, atrial fibrillation, or cardiac arrest at WHI baseline or occurrence of the incident events between WHI baseline and WHISCA enrollment. These incident events, including myocardial infarction, angina, congestive heart failure, coronary revascularization, carotid artery disease, coronary heart disease, and peripheral artery disease, were ascertained through central adjudication.

Domain-specific cognitive assessments

Detailed cognitive assessments occurred annually at each WHISCA visit. The battery of cognitive measures included the Primary Mental Abilities Vocabulary test (PMAVT) to assess verbal knowledge; letter and semantic fluency tests to assess verbal fluency; the Benton Visual Retention Test (BVRT) to assess short-term figural memory; the California Verbal Learning Test to assess verbal memory; the Digit Span Forward and Backward Test to assess attention and working memory; the Card Rotations Test to measure spatial ability; the Finger Tapping Test to assess fine motor speed; and the Modified Mini-mental State (3MS) examination to assess global cognitive function.

Covariates

Demographic information, medical history and lifestyle variables (including smoking and alcohol use) were obtained by self-report and clinical measurements using standardized study forms as detailed elsewhere. Current use of antidepressant medications was obtained through a medication inventory conducted at clinic visits. HT assignment was based on whether women were randomized to intervention arms or the placebo groups in the WHI-HT trials. Prior HT use was based on self-report at WHI baseline. History of stroke and transient ischemic attack (TIA) were collected via self-report at WHI baseline and by central adjudication until WHISCA enrollment.

Statistical Analysis

Women classified with and without elevated DS at WHISCA enrollment were compared with respect to demographic, lifestyle, cognitive, and clinical characteristics with chi-square tests and *t* tests.

Eight cognitive domains (global function, verbal knowledge, verbal fluency, figural memory, verbal memory, attention/working memory, spatial ability, and fine motor speed) were assessed. Individual scores on each outcome measure were first standardized by dividing their difference from the cohort-wide mean at WHISCA enrollment by their standard

deviation (SD). For cognitive domains based on more than one outcome measure, the standardized scores of these outcomes were averaged and renormalized. Scores from the BVRT were subtracted from zero so that higher scores signified better performance, consistent with scores for other domains. The analysis focused on assessing three features of the data: 1) whether there was a difference in cognitive function scores associated with DS at WHISCA enrollment (cross-sectional), 2) whether such a difference persisted over follow-up (longitudinal pattern or average scores over time), and 3) whether the magnitude of the difference changed over time (longitudinal change from baseline). Additional modeling was carried out to examine the relationship of persistent and fluctuating levels of DS with domain-specific cognitive changes over time, with and without omitting 81 women who developed MCI or probable dementia during follow-up. This analysis was based on women who had a cognitive assessment at one-year follow-up in addition to enrollment, permitting classification into three groups: women without elevated DS at either time-point; with fluctuating DS; and with persistently elevated DS.

Analysis of covariance (ANCOVA) was used for cross-sectional comparisons. A mixed-model repeated measures ANCOVA incorporating within person correlation was employed to assess whether mean cognitive domain scores and changes from WHISCA initial assessment in scores varied between women with and without DS. We assessed the significance of interaction terms between DS and prior CVD and between DS and CVRF score to explore whether the effects of DS on cognitive domain scores were moderated by either of these two factors. Models included adjustment for potential confounders (age, race/ethnicity, education, marital status, hysterectomy, antidepressant use, prior HT use, smoking, use of cholesterol-lowering medication, alcohol use, body mass index (BMI), hypertension, diabetes, prior CVD including TIA or stroke, physical activity, and treatment arm). The baseline score for each cognitive domain was included as a covariate for the change from baseline in the longitudinal analysis. Because these analyses were exploratory and the cognitive variables are inter-correlated, Type I error was not controlled for multiple outcomes. $P<0.01$ was considered significant. Statistical analyses were performed with SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Of the 2221 participants, 204 (9.2%) women met criteria for elevated DS at WHISCA baseline. Women with elevated DS were more likely to be African-American, have lower education, endorse a history of hysterectomy, diabetes mellitus, past alcohol use, be obese, report being on antidepressants, and less likely to be physically active **(Table 1)**. Among the 155 women reporting antidepressant use at baseline, 71 (46%) were taking selective serotonin reuptake inhibitors (DS: 8.3%; no DS: n=2.7%); 61 (39%) were taking tricyclic antidepressants (DS: n=2.5%; no DS: n=2.8%); and 23 (15%) were taking other classes or were on combination therapy (DS: n=1.96%; no DS: n=0.9%). Women with elevated DS at baseline had significantly lower raw scores on all cognitive measures except fine motor speed **(Table 2)**. Follow-up averaged 5.04 years (range: 0 to 7.50; Mean (SD) length of follow-up for DS: 5.10 (2.07); no DS: 4.46 (2.24); p < 0.0001).

Figure 1 summarizes the mean covariate-adjusted decline in cognitive domain test scores associated with elevated DS (relative to no symptoms) based on the cross-sectional and longitudinal analyses, with the differences averaged across time for the overall longitudinal pattern as well as for the changes from baseline. Elevated DS were associated with lower mean baseline scores in domains including verbal knowledge and verbal memory (p<0.01), figural memory (p<0.001) and visuospatial abilities (p<0.0001). The overall longitudinal pattern also showed lower scores for women with elevated DS: most significant differences were noted for global cognition, verbal knowledge, figural memory and visuospatial abilities (p<0.001), followed by verbal memory (p<0.01). In terms of change from baseline, global cognitive function (p<0.01) declined over time in women with elevated DS.

We performed additional analyses to examine the relationship of persistent and fluctuating levels of elevated DS with domain-specific cognitive changes over time. Women were classified into those without elevated DS at either time-point (N=1752); with fluctuating DS (N=202); and with persistently elevated DS (N=92). Mean GDS scores for these groups at baseline were 0.86, 3.90, and 7.32, respectively. At baseline, The fluctuating DS group was more likely to have lower education, be physically inactive, endorse a history of past drinking and be on antidepressants, whereas the persistent DS group was more likely to have lower education, poorer 3MS scores and diabetes, endorse current smoking and past drinking histories, be non-white, physically inactive and on antidepressants, relative to controls (p<0.01).

After full covariate adjustment, women with persistently elevated DS showed greater longitudinal declines in global cognition, verbal knowledge, and verbal fluency (p<0.01), and a trend in figural memory (p<0.05), whereas fluctuating DS course showed no changes (**Figure 2**). After excluding women who developed MCI/probable dementia (N=81) during follow-up, the persistent DS group findings slightly diminished but remained significant whereas the fluctuating DS group results enhanced slightly. The above results remained essentially unchanged after we repeated the longitudinal analyses controlling for the mean length of follow-up time since baseline.

Moderating effects of CVRF and CVD on DS-cognitive change relationships

We found significant interactions at WHISCA baseline between DS and CVD on figural memory and fine motor speed (p < 0.01), where women with CVD and DS performed worse than each of the other three groups (**Table 3**). However, no interactive effects of DS with CVD and CVRF scores on the longitudinal cognitive changes were observed. Since the CVRF model used here did not include cholesterol status, we conducted additional analyses and found no significant depressive symptoms-high cholesterol interactions on multiple domain cognitive function (p >0.05).

DISCUSSION

While elevated DS were cross-sectionally associated with multi-domain cognitive deficits, significant associations with longitudinal declines were only observed for global cognition in a cohort of community-dwelling postmenopausal women free of pathological cognitive impairment at baseline. However, women with persistently elevated DS showed greater

declines in global cognition and non-memory measures, and a trend in episodic memory measures whereas those with fluctuating DS course had no changes during follow-up. CVD and CVRF severity histories did not moderate the longitudinal DS-cognitive change relationships.

Elderly women with elevated DS performed poorly on several memory and non-memory-cognitive domains at baseline and longitudinal patterns over time. Our observations in this well-characterized sample of elderly women with elevated DS largely mirror findings reported in those with syndromal LLD. Nondemented acutely depressed older adults who perform poorly in memory and executive function measures at baseline may have coexisting MCI and be at higher risk for developing dementia at follow-up, when compared to those with acute LLD who remain cognitively normal over time. Our findings suggest that DS, regardless of the severity, frequently co-exist with cognitive deficits that do not meet the criteria for MCI and probable dementia, although the consequence of this co-morbidity is unclear.

The present study findings that elevated DS are related to declines in global cognition measure is consistent with some, but not all studies. The inconsistencies in findings may be due to the fact that the DS-cognitive decline associations reported previously are largely driven by the course of depressive symptomatology. Our observations of persistent DS being associated with nonmemory declines over time are in accordance with previous mid- and late life studies. The vulnerability to the effects of elevated DS on executive function measures appears to be greatest with symptom chronicity and advanced age. Elevated DS is likely to persist over time in some older adults, and the risk of developing major depression is significantly higher at follow-up. Persistence of LLD is associated with multiple domain cognitive deficits at baseline, suggesting that the presence of baseline cognitive impairment may be prognostic indicators of LLD outcomes. We extend these prior observations to a cohort of postmenopausal women with milder depressive symptoms, suggesting that both subclinical and syndromal DS, if persistent, can increase the risk of future cognitive decline.

Our observations that fluctuating levels of DS do not detrimentally affect multiple cognitive measures are consistent with the literature. On the contrary, remission of DS and syndromal depression has been associated with MCI and probable dementia among elderly women and in mixed gender studies. The fluctuating DS course is likely reflective of symptom remission due to the changes in psychosocial stressors, physical ailments and/or remission of depression. We are unable to disentangle the association of these factors with the changes in DS status in this study.

The observations that the CVRF and CVD histories did not detrimentally alter cognitive measures over time in women with DS underscore the complexities in the pathophysiological mechanisms linking DS with subsequent cognitive decline. While our results are also consistent with some studies, detrimental effects on cognition when depression co-exists with certain CVRFs have been previously reported. For instance, the relationship of depression with incident cognitive impairment was affected by diabetes in a previous study. Executive dysfunction is associated with orbitofrontal volume loss in depressed diabetics. Higher CVRF scores have also been shown to predict lesser recovery of

working memory deficits and executive dysfunction to treatment in LLD. Persistent DS in patients with coronary heart disease may increase the risk of future cognitive decline. The DS chronicity after acute coronary syndrome may be associated with decreased white matter integrity in the anterior cingulate, though these findings were no longer significant after controlling for CVRFs. While we did not find an interactive relationship of DS with CVRF scores and CVD on cognitive decline, a few points are worthy of mention. First, the smaller sample size in the persistent DS group precluded us from examining the effects of CVRFs and CVD when comorbid with chronic DS on cognition. Second, we did not examine the interactive relationship of DS and individual vascular risk factors separately, rather calculated the CVRF score for each individual by using an all-inclusive model. Therefore, it is still possible that late-life DS, especially when chronic and occurring in those with specific vascular risk factors (for e.g. in diabetics) and coronary heart disease may result in accelerated declines in different cognitive domains. This should be the focus of future investigations.

The lack of influence of CVRF score severity and CVD on the DS-associated memory decline also suggests that this relationship may be mediated by medial temporal lobe neurodegeneration and non-vascular etiologies. LLD is associated with hippocampal volume loss from excessive stress-related glucocorticoid release. Also, amyloid and neurofibrillary tangles, genetic heritability, proinflammatory cytokines and oxidative stress have been implicated in the mechanistic underpinnings of both LLD and AD.[ ][ ] Since DS in the elderly population is a heterogeneous syndrome, future studies that examine the association of DS with incident cognitive impairment should carefully delineate older depressed adults into subtypes based on co-morbidity and neuropsychological deficits.

The strengths of this study include the well-characterized cohort of high functioning, healthy elderly women, the large sample size, the availability of annual domain-specific cognitive measurements and the ability to adjust for multiple potential confounders. However, several limitations need to be addressed. First, since we relied on self reported GDS scores to define DS, it is possible that some women may have met major depressive disorder criteria on a structured clinical interview. Regardless, the mean GDS scores even in women who had persistent DS were in the milder range and therefore the vast majority of women with positive scores had subclinical DS. Second, we are unable to comment on the effects of the age of onset, current episode duration, and number of prior episodes on our study findings. Recent evidence suggests that later onset depression may be a prodromal manifestation of AD, whereas recurrent DS with onset in mid-life may increase the risk of vascular dementia. Third, persistent and fluctuating levels of DS were defined based only on two GDS measures similar to prior studies. We primarily took this approach due to missing GDS measurements at follow-up and to prevent sample size attrition. Fourth, antidepressant use was associated with attention/working memory, figural memory and fine motor speed ($p < 0.05$) at baseline. Although we controlled for baseline antidepressant use, we did not include follow-up medication data in our analyses. Future studies should define persistence and fluctuations of DS based on measurements at multiple timepoints, and also factor in the effects of follow-up antidepressant use history on the DS-cognitive health relationships. Fifth, the sample size in the persistently elevated DS group is relatively small, and may have influenced our findings. Sixth, the CVRFs and CVD history was ascertained by self-report, which may have resulted

in inaccurate estimation and misclassification of these conditions, and may have reduced the strength when examining for interactions. Sixth, our sample is not population-based and included women who participated in a HT trial, which limit the generalizability of our findings. Finally, since this study was largely exploratory, adjustments were not carried out for multiple comparisons.

In conclusion, persistent DS course resulted in greater declines affecting multiple cognitive domains in our elderly women cohort. CVRF and CVD histories do not appear to influence the association of DS with cognitive decline. A differential course of managing DS in an attempt to reduce the risk of cognitive decline may not be warranted for women with CVRFs and CVD. Future prospective studies should confirm our findings and determine if treatment of DS will reverse cognitive deficits in those women with different degrees of CVRF and CVD severity.

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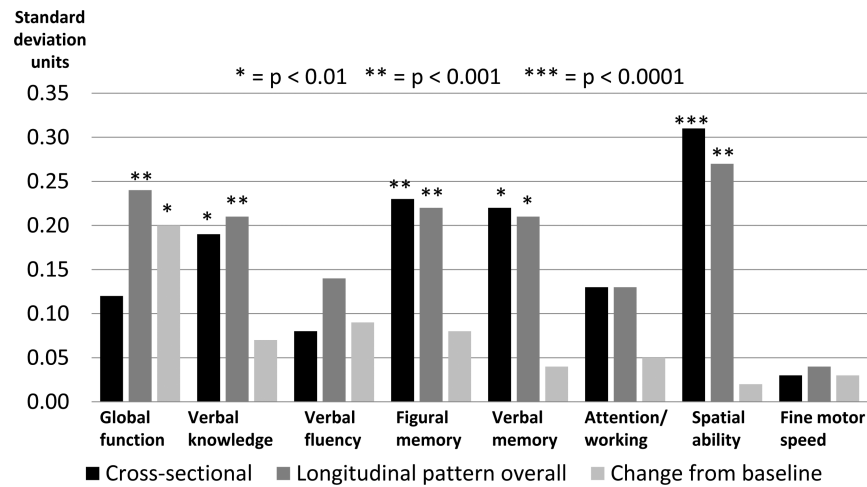
Figure 1.
Mean decrements associated with elevated depressive symptoms for cognitive domains [a]
Abbreviation: DS: depressive symptoms.

[a] With adjustment for age, race/ethnicity, education, marital status, hysterectomy, current use of antidepressant medications, prior use of hormone therapy, smoking, use of cholesterol-lowering medication, alcohol use, body mass index, hypertension, prior cardiovascular/cerebrovascular disease including stroke or transient ischemic attack, diabetes, physical activity, and Women's Health Initiative hormone therapy trial treatment arm. Cross-sectional refers to baseline differences; longitudinal pattern overall refers to mean differences across time; change from baseline refers to differences in changes from baseline averaged across time.
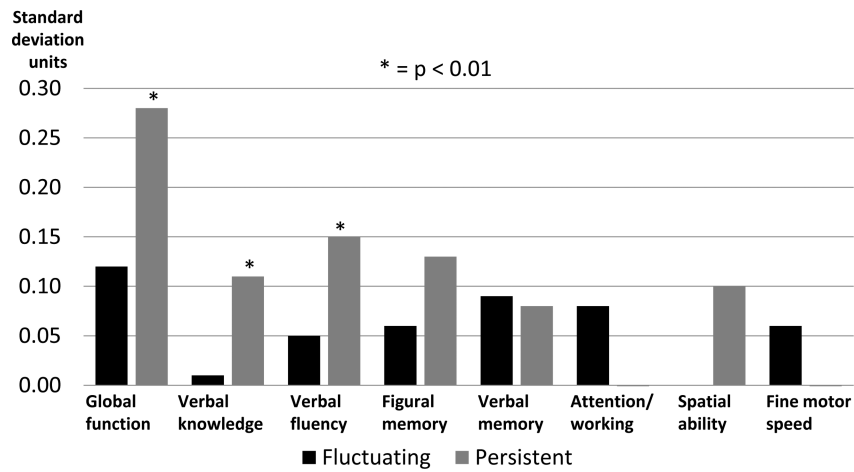
Figure 2.
Mean longitudinal domain-specific cognitive changes from baseline associated with fluctuating and persistently elevated depressive symptoms versus no symptoms [a]
[a] With adjustment for age, race/ethnicity, education, marital status, hysterectomy, current use of antidepressant medications, prior use of hormone therapy, smoking, use of cholesterol-lowering medication, alcohol use, body mass index, hypertension, prior cardiovascular/cerebrovascular disease including stroke or transient ischemic attack, diabetes, physical activity, mean length of follow-up time from baseline, and Women's Health Initiative hormone therapy trial treatment arm.

Table 1

Baseline characteristics for WHISCA cohort by depressive symptom status

Characteristic	No Depressive Symptoms N=2017	Elevated Depressive Symptoms N=204	p-value
Age, years, n (%)			0.96
65-69	955 (47)	95 (46)	
70-74	740 (37)	77 (38)	
75-80	322 (16)	32 (16)	
Education, n (%)			< 0.01
< high school grad/GED	91 (5)	16 (8)	
High school grad/GED	422 (21)	55 (26)	
Some college	834 (41)	86 (42)	
College grad	670 (33)	47 (23)	
Race/ethnicity, n (%)			< 0.0001
African American	111 (6)	26 (13)	
Caucasian	1835 (91)	167 (82)	
Other	71 (4)	11 (5)	
Marital status, n (%)			0.35
Never married	64 (3)	7 (3)	
Separated/divorced	231 (11)	32 (16)	
Widowed	603 (30)	59 (29)	
Married	1119 (55)	106 (52)	
Alcohol use, n (%)			< 0.0001
Nondrinker	247 (12)	19 (9)	
Past drinker	613 (31)	93 (46)	
Current drinker	1150 (57)	91 (45)	
Smoking, n (%)			0.27
Never	1107 (55)	114 (56)	
Past	793 (39)	73 (36)	
Current	117 (6)	17 (8)	
Leisure physical activity, MET, n (%)			<0.001
Lowest tertile	649 (32)	94 (46)	
Mid tertile	674 (33)	61 (30)	
Highest tertile	694 (34)	49 (24)	
Body mass index, kg/m^2, n (%)			< 0.01
< 25	579 (29)	44 (22)	
25-29	749 (37)	69 (34)	
30+	689 (34)	91 (45)	
Hypertension, n (%)	1094 (54)	104 (51)	0.37
Diabetes mellitus, n (%)	171 (8)	31 (15)	< 0.01
Dyslipidemia, n (%)	353 (18)	34 (17)	0.76
Cardiovascular disease, n (%)	304 (15)	35 (17)	0.43
Stroke or TIA, n (%)	89 (4)	9 (4)	1.00

Characteristic	No Depressive Symptoms N=2017	Elevated Depressive Symptoms N=204	p-value
Prior hysterectomy, n (%)	761 (38)	92 (45)	0.04
Current use of antidepressant medications, n (%)	129 (6)	26 (13)	< 0.001
Prior hormone therapy, n (%)	918 (46)	103 (50)	0.17
WHI treatment assignment, n (%)			0.64
Active	984 (49)	96 (47)	
Placebo	1033 (51)	108 (53)	

Abbreviations: WHI: Women's Health Initiative; WHISCA: Women's Health Initiative Study of Cognitive Aging; MET: Metabolic Equivalent of Task; TIA: Transient Ischemic Attack.

Table 2

Cognitive test scores at WHISCA enrollment by depressive symptom status

Mean (standard deviation)	No Depressive Symptoms N=2017	Elevated Depressive Symptoms N=204	p-value
Global function			
3MS	97.03 (2.73)	95.97 (3.52)	< 0.0001
Verbal knowledge			
PMAVT	37.10 (9.51)	33.35 (10.00)	< 0.0001
Verbal fluency			
Category	29.15 (6.19)	27.99 (6.17)	0.01
Letter	40.01 (12.45)	38.08 (12.78)	0.04
Figural memory			
BVRT	−6.89 (3.58)	−8.26 (4.52)	< 0.0001
Verbal memory			
CVLT-a	28.94 (6.23)	27.10 (6.41)	< 0.0001
CVLT-b	6.61 (2.12)	6.05 (2.08)	< 0.001
CVLT free short delay	8.54 (3.03)	7.56 (3.29)	< 0.0001
CVLT free long delay	9.28 (2.99)	8.50 (3.17)	< 0.001
Attention/working memory			
Digit forward	7.50 (2.06)	7.05 (2.00)	< 0.01
Digit backward	6.73 (1.99)	6.34 (2.18)	< 0.01
Spatial ability			
Card rotation	56.25 (27.33)	45.74 (26.87)	< 0.0001
Fine motor speed			
Tapping dominant	38.65 (7.60)	37.83 (8.11)	0.15
Tapping non-dominant	36.58 (6.40)	35.83 (6.81)	0.12

Abbreviations: WHISCA: Women's Health Initiative Study of Cognitive Aging; 3MS: Modified Mini-Mental State Examination; PMAVT: Primary Mental Abilities Vocabulary test (PMAVT); BVRT: Benton Visual Retention Test; CVLT: California Verbal Learning Test.

Table 3

Interaction effect of depressive symptoms and cardiovascular disease on cognitive domains at baseline[a]

Depressive Symptoms/CVD	No Depressive Symptoms CVD Negative		No Depressive Symptoms CVD positive		Elevated Depressive Symptoms CVD Negative		Elevated Depressive Symptoms CVD Positive		p-value
Cognitive domain	Adjusted mean	Standard error	Adjusted mean	Standard error	Adjusted mean	Standard error	Adjusted mean	Standard error	
Global function	0.07	0.02	0.06	0.05	−0.05	0.06	−0.09	0.14	0.85
Verbal knowledge	0.06	0.02	−0.02	0.05	−0.08	0.07	−0.41	0.15	0.18
Verbal fluency	0.01	0.02	0.11	0.06	−0.01	0.07	−0.24	0.16	0.07
Figural memory	0.05	0.02	0.04	0.05	−0.09	0.07	−0.57	0.15	<0.01[b]
Verbal memory	0.06	0.02	0.00	0.06	−0.15	0.07	−0.26	0.16	0.73
Attention/working memory	0.03	0.02	0.04	0.06	−0.03	0.08	−0.47	0.17	0.02
Spatial ability	0.04	0.02	0.04	0.06	−0.19	0.07	−0.61	0.16	0.02
Fine motor speed	0.01	0.02	0.06	0.06	0.07	0.08	−0.41	0.17	<0.01[b]

Abbreviations: CVD: Cardiovascular disease; HT: Hormone Therapy; TIA: Transient Ischemic Attack.

[a] With adjustment for age, race/ethnicity, education, marital status, hysterectomy, current use of antidepressant medications, prior use of Hormone Therapy, smoking, use of cholesterol-lowering medication, alcohol use, body mass index, hypertension, cardiovascular/cerebrovascular disease including stroke or transient ischemic attack, diabetes, physical activity, and Women's Health Initiative hormone therapy trial treatment arm.

[b] Women with elevated depressive symptoms and cardiovascular disease performed worse than each of the other 3 groups for figural memory and fine motor speed (p < 0.01).