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The relationship between optimism, MCI, and dementia among postmenopausal women

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Abstract

Objectives: The relationship between optimism and cognitive functioning is not fully understood. We examined the association of optimism with risk of mild cognitive impairment (MCI) and dementia in the Women's Health Initiative Memory Study (WHIMS).

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Conflicts of Interest

BCS, GLW, JL, SRR, SAS, GAB, AHS, SAG, RC, JWW, JCC and KMH have no conflicts to declare. Rowan T. Chlebowski is a consultant for Novartis, AstraZeneca, Genentech, Merck, Immunomedics, Puma and received honorarium from Novartis and AstraZeneca.

ClinicalTrials.gov Identifiers: NCT00017953 (WHIMS-Y); NCT01124773 (WHIMS/WHIMS-ECHO).

Methods: Optimism was measured by the Life Orientation Test-Revised (LOT-R) total score, and optimism and pessimism subscales. A panel of experts adjudicated cognitive endpoints based on annual cognitive assessments. We used cox proportional hazard regression models to examine the association of LOT-R total score and optimism and pessimism sub-scores with MCI/dementia. We also examined whether the relationship between vascular disease, LOT-R total score, optimism and pessimism, and cognition.

Results: Mean age was 70.5 (SD=3.9) years. The sample (N=7249) was 87% white, and 29.8% of participants had < 12 years of education. Total LOT-R score (HR=0.96, 95% CI: 0.94, 0.98, p<0.001) was associated with lower risk of combined MCI or dementia. More pessimism (HR=1.08, 95% CI: 1.05, 1.11, p<0.0001) was associated with higher risk of MCI or dementia after adjustment for ethnicity, education, vascular disease, and depression. No significant relationships emerged from the optimism subscale.

Conclusion: These data suggest that less pessimism, but not more optimism, was associated with a lower risk of MCI and dementia.

Keywords

LOT-R; optimism; pessimism; dementia; MCI

Introduction

Worldwide, nearly 50 million people have a diagnosis of dementia (World Health Organization, 2019). With almost 10 million new cases diagnosed annually, dementia remains a critical and urgent public health concern. Researchers and clinicians are making headway in understanding more about the underlying diseases and even identifying personal resilience factors—that is, traits or behaviors that confer some protection against cognitive impairment, including dementia, for those at highest risk, such as educational and occupational attainment and time spent engaging in leisure activities (Ferrari et al., 2013).

Mounting evidence also suggests that dispositional and personality factors may play a role in cognitive health in late life. Specifically, personality traits such as agreeableness, conscientiousness, and extraversion have been related to preservation of late-life cognitive health, and a lower risk of developing cognitive impairment and dementia, while high levels of neuroticism in particular have been associated with an increased risk for late life cognitive decline, mild cognitive impairment (MCI), and dementia (Aschwanden et al., 2020; Cyprien et al., 2021; Low et al., 2013; Sutin et al., 2018; Terracciano & Sutin, 2019). An increased risk of dementia has also been linked to traits and characteristics such as cynicism, hostility, negative affect, and hopelessness, even after current depressive symptoms have been accounted for. However, longstanding depressive symptoms have also been independently related to the development of dementia in later life as well (Cherbuin et al., 2015; Katon et al., 2015; Korhonen et al., 2022; Larsen et al., 2022).

In the last decade, there has been an increasing interest in the role that dispositional optimism, a construct related to positive expectancy and hope about the future as well as ones' own self-efficacy, may play in successful aging, especially given evidence

that optimism may mediate the relationship between personality factors and quality of life(Carver & Scheier, 2014; Serrano et al., 2020). Evidence from recent studies points to optimism as an additional possible resilience factor against cognitive impairment (Gawronski et al., 2016; Taber et al., 2016). For instance, in a sample of 326 cancer survivors aged 24–96 in the 3rd cycle of the 4th Health Information National Trends Survey, generalized (trait) optimism and spontaneous self-affirmation were inversely associated with likelihood of cognitive impairment. Unfortunately, the study used only one item from the Revised Life Orientation Test (LOT-R) to measure generalized optimism: "I'm always optimistic about my future", and cognitive decline was measured subjectively by asking, "Because of a physical, mental, or emotional condition, do you have serious difficulty concentrating, remembering, or making decisions?" The researchers found that each standard deviation increase in optimism was associated with 64% lower odds of reported cognitive impairment (OR: 0.36; 95% CI: 0.23, 0.55) (Taber et al., 2016). While there are a number of limitations of this study, including its' cross-sectional design, low sample size, and lack of adjudicated cognitive outcomes, it highlights a research question that deserves further investigation. Another study prospectively examined the association of LOT-R total score with global cognition, measured by the Telephone Interview for Cognitive Status (TICS), a measure of global cognitive function, over four years of follow-up with participants from the Health and Retirement Study (HRS). Results indicated a one standard deviation increase in LOT-R score was associated with a 30% lower odds of cognitive impairment over the 4-year follow-up period (OR: 0.70, 95% CI: 0.61–0.81); a dose-response relationship pattern emerged (Gawronski et al., 2016). Interestingly, the LOT-R optimism and pessimism subscales were not examined separately.

There are assuredly intermediate factors, both behavioral and biological, potentially linking optimism (and pessimism) with cognitive impairment and dementia. For example, coronary heart disease and overall cardiovascular health have been linked with both optimism and cognition (Boehm et al., 2018; Matthews et al., 2004). Findings from a sample of 97,253 women in the Women's Health Initiative (WHI), followed over 5 years, reveal that optimists had a lower hazard of coronary heart disease (CHD; adjusted hazard ratio: 0.91; 95% CI 0.83, 0.99) and of CHD-related mortality (HR: 0.70; 95% CI 0.55, 0.90) compared with their more pessimistic counterparts (Tindle et al., 2009). Cardiovascular disease is a well-established risk factor for cognitive decline (Meissner, 2016; Novak & Hajjar, 2010; Walker et al., 2017), and evidence from 6,044 adults aged 50+ in the HRS indicates that for each one-unit increase in optimism, as measured by the LOT-R, a person has a 10% lower likelihood of having a stroke (OR: 0.90; 95% CI: 0.84 to 0.97) (Kim et al., 2011). In contrast, pessimists have been found to be more likely to have evidence of cardiovascular and cerebrovascular disease, the latter of which is a well-documented risk factor for dementia among older adults (Iadecola, 2014; Nabi et al., 2010; M. T. Pankalainen et al., 2015; Perrotta et al., 2016).

In this study, we examined the relationship between the LOT-R score, a measure thought to measure dispositional optimism, and MCI or dementia in the Women's Health Initiative Memory Study (WHIMS). Because debate remains about whether the LOT-R measures two ends of a unipolar construct (more or less optimism)(Cano-Garcia et al., 2015) or in contrast, a bipolar construct (optimism and pessimism)(Glaesmer et al., 2012; Hinz et al., 2017), we

also separately examined the subcomponents of the LOT-R, therefore assessing optimism and pessimism independently. By examining both optimism and pessimism we attempt to disentangle these two components allowing us to answer the question, “Is high optimism or low pessimism protective of cognitive function?” (Carver et al., 2010). Prospective annual cognitive assessments and adjudicated MCI and dementia outcomes in WHIMS offered a unique opportunity to test the hypothesized association more rigorously than in some previous investigations in which cognitive outcome was algorithmically assessed.

Materials and Methods

Participants

The Women’s Health Initiative Memory Study (WHIMS), an ancillary study to the WHI Hormone Trials, enrolled 7,479 women between the ages of 65 to 79 years from 1995 to 1999. The Institutional Review Board at each clinic site approved the consent forms, and written informed consent was obtained from all participants. The study design has been published previously (Anderson et al., 2004; Rapp et al., 2003; Shumaker et al., 2004; Shumaker et al., 2003; Shumaker et al., 1998). WHIMS was designed to study the effects of post-menopausal hormone therapy on the incidence of probable dementia and mild cognitive impairment (MCI), and global cognitive function in parallel clinical trials. The trials compared conjugated equine estrogen alone (E-alone) in women with a hysterectomy, or estrogen (E) combined with medroxyprogesterone acetate (progestin [E + P]) with respective placebo groups. Annual cognitive screening, comprehensive clinical and neurocognitive exams for participants screening positive, and other information collected from participants and knowledgeable friends or family members were used in central adjudication (described below) by specialists who classified women as having no cognitive impairment, MCI, or probable dementia. Participants were followed after the trials ended in 2002 (E + P) (Rapp et al., 2003; Shumaker et al., 2003) and 2004 (E-alone) (Anderson et al., 2004; Shumaker et al., 2004) with annual in-person cognitive assessments until 2007–2008, at which time the study transitioned to telephone cognitive assessments, which are currently ongoing. All WHIMS participants, except those with dementia at baseline, were eligible for inclusion in this analysis.

LOT-R

The LOT-R is the most widely used instrument used to assess ‘dispositional optimism’ (Scheier et al., 1994). The self-report inventory includes 10, five-point Likert-style questions; six items contribute to the score and four items are filler items. The total score is calculated by reverse scoring three items (#3. “If something can go wrong for me, it will”; #7. “I hardly ever expect things to go my way”; and #9. “I rarely count on good things happening to me”) and summing across all six items.

Originally, the scale was thought to measure a unidimensional, single factor (optimism) and authors initially conceptualized high and low scores as representing two poles of a continuum representing a single construct. However, more recent studies have suggested that the LOT-R may measure two distinct and independent constructs, optimism and pessimism (Carver & Scheier, 2014; Glaesmer et al., 2012; Herzberg et al., 2006; Hinz et al., 2017). As

such, we chose to include examine the total LOT-R score and ‘optimism items’ (sum of three optimism items), and ‘pessimism items’ (sum of three pessimism items) sub-scores.

Cognitive Assessment

WHIMS had two stages. Stage one was the active intervention period (1996–2006) and stage two is a follow-up observational period which continues through today. During the active intervention period, participants were administered the Modified Mini-Mental State Exam (3MS) annually (Teng & Chui, 1987). Women scoring below pre-determined age- and education-adjusted cut points were referred for a clinical evaluation by a board-certified physician and neuropsychological testing. Testing included portions of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) battery (Morris et al., 1989), the Mini Mental State Exam (MMSE) (Folstein et al., 1975), the Trail Making Test Parts A and B (Reitan, 1958), a structured psychiatric interview(Spitzer, Williams, Kroenke, & et al., 1994), and questions about depressive symptoms. A knowledgeable informant completed the Acquired Cognitive and Behavior Changes (ACBD) (Spitzer, Williams, Kroenke, Linzer, et al., 1994) interview. A central panel of dementia experts, blind to treatment assignment (and LOT-R results), then adjudicated cases, classifying participants as cognitively normal or having MCI or probable dementia according to standard criteria (American Psychiatric Association, 1994; Petersen et al., 1994). In the WHIMS observational extension period (2007-present), a validated telephone cognitive battery (Rapp et al., 2012) was administered annually to all participants comprising a modified version of the Telephone Interview for Cognitive Status (TICS-m) (Brandt et al., 1988), the Oral Trail Making Tests Part A and B (Ricker & Axelrod, 1994), the East Boston Memory Test (Gfeller & Horn, 1996), Digit Span (Wechsler, 1987), and Verbal fluency/Animals (Benton, 1968). When participants scored below 31 points on the TICS-m, the Dementia Questionnaire (Kawas et al., 1994) was administered to an informant to evaluate functional status. Cognitive status was then adjudicated as no impairment, MCI, or probable dementia as described above.

Predictors

At baseline, participants reported their age, race/ethnicity, and education level. Health history included history of stroke, cardiovascular disease, hypertension, diabetes, high cholesterol treated with medication, and smoking. Hormone therapy (HT) study arm and the region of the US from where the participant was recruited were included as covariates. Scores on the Burnam depression screener (Burnam et al., 1988), which includes items from the Center for Epidemiologic Studies-Depression Scale (Weissman et al., 1977), were used to quantify depressive symptom severity. The Burnam screener weights test items to provide improved sensitivity and positive predictive value for detecting depressive disorders. MET-hours per week from walking was calculated using weight and data from a standardized questionnaire that asked participants about walking outside the home including questions about frequency, speed, and duration of walking during an average week.

Statistical Analysis

Descriptive statistics were used to compare women across quartiles of LOT-R, ‘optimism items sub-score’, and ‘pessimism items sub-score’ on demographic variables, medical history, health behaviors, HT study arm, region of the country, and medical variables

using general linear models for continuous variables and chi-squared tests for categorical variables. Cox proportional hazards regression models were used to assess the time to occurrence of probable dementia. Women who were not classified with dementia or who had not died by their last (most recent) visit were censored. Women who died during the study period were censored at the time of their last cognitive assessment. We also examined MCI and a composite of probable dementia and MCI as outcomes. Race/ethnicity and education were tested as potential effect modifiers using statistical interactions. All hypothesis tests were 2-sided and performed at the α=.05 level of significance. All analyses were performed using SAS version 9.4 (SAS Institute, Cary).

Results

Data from a total of 7,479 women were available for this study. After exclusion of women with incomplete data on our primary variables, the analysis included a total of 7,249 women. Women were followed for a median of 9.06 (IQR 6.02–17.54) years and there were 725 cases of probable dementia, 825 cases of MCI, and 1281 cases of either probable dementia or MCI. Demographic characteristics of participants by quartile of LOT-R scores are presented in Table 1a. Characteristics of the women are also presented by quartiles of ‘optimism items’ and ‘pessimism items’ subscale scores in Tables 1b and 1c.

When examining by quartiles, higher LOT-R score was significantly associated with higher proportion of white race/ethnicity, higher education, lower prevalence of cardiovascular disease, hypertension, and diabetes, lower depression, lower prevalence of high cholesterol, lower BMI, higher rates of never smoker, and more MET-hours per week from walking. Similar patterns existed for quartiles of ‘optimism items’ sub-scores with the exception of hypertension, diabetes, and HT arm (Table 1b). For quartiles of ‘pessimism items’ sub-scores, we see the reverse relationships with LOT-R quartiles with the exception of high cholesterol (Table 1c).

As seen in Table 2 results from Cox proportional hazards models, the higher LOT-R score was significantly associated with lower risk of probable dementia (HR 0.97; 95% CI, 0.94–0.99; p=0.0101), MCI (HR 0.97; 95% CI, 0.95–0.99; p=0.0064), and the combined outcome of probable dementia/MCI (HR 0.96; 95% CI, 0.94–0.98; p<0.0001). The sub-score of pessimism items was inversely related to cognitive outcomes, such that higher levels of pessimism were associated with greater risk of cognitive impairment. There were no significant relationships between ‘optimism items’ sub-score and probable dementia, MCI, or the combined outcome of probable dementia and MCI. There were no significant interactions between race/ethnicity or education and the either LOT-R, optimism items sub-score, or pessimism items sub-score when examining probable dementia, MCI, or the combined outcome of probable dementia and MCI (Table 3).

Discussion

Results from this study suggest that total LOT-R score is related to cognitive outcomes in our sample of elderly women. Specifically, women with higher overall LOT-R scores have a lower likelihood of being classified as having MCI or probable dementia – a

finding that suggests that optimism is the key driver in protecting against late life cognitive decline. However, when LOT-R scores were deconstructed into their subscales comprised of optimism items and pessimism items alone, a relationship with pessimism, but not optimism, remained. Specifically, individuals who endorsed more pessimism had a greater likelihood of being classified as having MCI or probable dementia, but there was no significant relationship between optimism alone and MCI/probable dementia. In our sample, a 1-point increase on the pessimism subscale was associated with an approximate 8% increase in the likelihood of receiving a classification of MCI or probable dementia. In the multivariable models, associations remained even after adjusting for variables known to be related to cognitive functioning, including age, race, education, CVD, and depressive symptoms.

These data suggest that lower levels of dispositional pessimism may be more important than high levels of optimism in protecting against MCI/dementia in late life. Findings are discordant with those showing optimism is related to cognitive function; however, many studies have used total LOT or LOT-R as a unidimensional measure of optimism alone, and have not examined optimism and pessimism items separately. Utilizing LOT-R score as a continuous metric of high versus low levels of optimism may produce results (such as our significant finding for total LOT-R score) showing a relationship between cognitive outcome and total score. The relationship with pessimism and not optimism items was identified only after examining the separate sub-components, a finding that perhaps also lends more support to the concept of the bi-dimensionality of the LOT-R (Glaesmer et al., 2012; Herzberg et al., 2006; Hinz et al., 2021). Other studies that did examine both facets of the LOT-R have also found relationships between pessimism (or the absence of it) and physical health variables, such as hypertension, CVD, stroke, insulin resistance and inflammation (Barnett & Anderson, 2020; Raikkonen et al., 1999; Scheier & Carver, 2018; Serlachius et al., 2015; Tindle et al., 2018). We found similar relationships between LOT-R, pessimism score, and hypertension, CVD, and diabetes in our sample, but were unable to directly test a mediation relationship in this study.

Ultimately, the relationship between optimism/pessimism, cognition, and vascular risk is likely complex, with both direct biological and indirect, behavioral mechanisms also at play. For instance, individuals who are more optimistic and less pessimistic not only have fewer medical conditions, but tend to be more proactive about exhibiting positive health related behaviors and addressing medical conditions or ailments. This includes seeking a healthy diet, engaging in regular exercise, and avoiding excessive substance use and tobacco (Donovan et al., 2017; Giltay et al., 2007; M. Pankalainen et al., 2018; Serlachius et al., 2015; Shepperd et al., 1996; Steptoe et al., 2006). Additionally, pessimists may have other behavioral-related risks for cognitive decline compared with their more optimistic counterparts. This includes having less social support, being more isolated and experiencing more anxiety and depression (Faye-Schjoll & Schou-Bredal, 2019; Schou et al., 2004), all of which are related to cognitive decline in late life (Carver et al., 2003; Holwerda et al., 2014; Hsiao et al., 2018; Penninkilampi et al., 2018; Poey et al., 2017; Shankar et al., 2013; Yin et al., 2019). A plethora of studies have found that, compared with optimists, pessimists are also perceived as being less likeable and more hostile, less likely to be part of a peer group, and are less satisfied with relationships than their optimistic counterparts (Luger et al., 2009; M. T. Pankalainen et al., 2015; Smith et al., 2013; Srivastava et al., 2006; Weber

et al., 2007). The presence of pessimism may therefore confer a unique collective risk for MCI/dementia, possibly through both biological and behavioral pathways.

This study has several limitations, including the fact that our sample was comprised exclusively of women and the relationship between pessimism, optimism, and MCI/dementia in late life may be different in men. Men may manifest optimism and pessimism differently than women, and in men, high levels of pessimism and/or low levels of optimism may be associated with more vascular disease and/or higher likelihood of developing dementia (Ikeda et al., 2011; M. Pankalainen et al., 2018; M. T. Pankalainen et al., 2015; Rozanski et al., 2019). Also, our sample was largely, though not exclusively, White and this pattern of findings needs to be replicated in more diverse samples to determine how cultural or sociodemographic factors may affect these relationships. Study strengths include the large sample size, prospective design and availability of deeply phenotyped cognitive data, including adjudicated cognitive outcomes.

Conclusion

Optimism was not associated with MCI/dementia in late life. In contrast, it appears that the absence of pessimism may be a more important attitudinal factor associated with lower risk of MCI/dementia. Future studies should examine whether the proposed behavioral factors, including, diet, exercise, and abstinence from tobacco and alcohol, are meaningful variables in the relationship between optimism/pessimism, cognition, and CVD.

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The following authors conducted the statistical analysis: Gaussoin SA

The following authors had major roles in the acquisition of the data: Shumaker S, Rapp SR, Chlebowski RT, Wactawski-Wende J.

The following authors interpreted the data and revised the manuscript for intellectual content: Sachs, BC, Hayden KM, Gaussoin SA, Brenes GA, Casanova, R, Chlebowski RT, Chen JC, Juhua Luo J, Rapp SR, Shadyab AH, Wells GW, Tindle HA, Shumaker S, Wactawski-Wende J.

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Data Availability

The data that support the findings of this study are available upon request from the Women's Health Initiative and the Women's Health Initiative Memory Study subject to study policies as well as privacy and ethical restrictions.

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Table 1a.

Characteristics of Participants by Quartile of LOT-R Score (n=7249)

	Quartile of LOT-R Score				
Subgroup	**1 (Lowest)**	**2**	**3**	**4 (Highest)**	**P-Value**
Demographic factors					
Age (mean, SD)	70.53 (3.86)	70.53 (3.88)	70.49 (3.83)	70.33 (3.77)	0.1374
Race/Ethnicity					<.0001
Black	162 (8.17%)	112 (5.81%)	105 (6.31%)	111 (6.69%)	
Other	181 (9.12%)	106 (5.50%)	72 (4.33%)	56 (3.38%)	
White	1641 (82.7%)	1710 (88.7%)	1487 (89.4%)	1492 (89.9%)	
Education > high school	1201 (60.6%)	1335 (69.3%)	1257 (75.5%)	1306 (78.8%)	<.0001
Medical History					
Stroke	39 (1.96%)	32 (1.66%)	27 (1.62%)	22 (1.33%)	0.5235
Cardiovascular Disease	243 (12.2%)	171 (8.86%)	135 (8.10%)	130 (7.83%)	<.0001
Hypertension	1061 (53.3%)	953 (49.4%)	793 (47.6%)	797 (48.0%)	0.0017
Diabetes	223 (11.2%)	153 (7.93%)	122 (7.32%)	111 (6.69%)	<.0001
Depression (Burnam; mean, SD)	0.07 (0.16)	0.02 (0.08)	0.02 (0.06)	0.01 (0.05)	<.0001
High Cholesterol	369 (18.8%)	381 (20.0%)	279 (16.9%)	271 (16.5%)	0.0232
BMI (mean, SD)	28.86 (5.88)	28.62 (5.80)	28.35 (5.66)	28.23 (5.42)	0.0003
Health Behaviors					
Smoking					0.0007
Never Smoked	1051 (53.4%)	975 (51.3%)	887 (54.0%)	888 (54.1%)	
Past Smoker	742 (37.7%)	800 (42.1%)	667 (40.6%)	628 (38.3%)	
Current Smoker	174 (8.85%)	124 (6.53%)	90 (5.47%)	124 (7.56%)	
MET-hours per week from walking	3.76 (5.46)	4.16 (5.42)	4.40 (5.59)	4.60 (6.05)	<.0001
HT Arm					<.0001
EPLC	450 (22.6%)	371 (19.2%)	293 (17.6%)	322 (19.4%)	
ERT	431 (21.6%)	378 (19.6%)	298 (17.9%)	304 (18.3%)	
PERT	535 (26.9%)	583 (30.2%)	531 (31.9%)	518 (31.2%)	
PPLC	576 (28.9%)	598 (31.0%)	545 (32.7%)	516 (31.1%)	
Region of Country					<.0001
Northeast	621 (31.2%)	498 (25.8%)	438 (26.3%)	384 (23.1%)	
South	406 (20.4%)	423 (21.9%)	341 (20.5%)	351 (21.1%)	
Midwest	456 (22.9%)	472 (24.5%)	417 (25.0%)	420 (25.3%)	
West	509 (25.6%)	537 (27.8%)	471 (28.3%)	505 (30.4%)	

Abbreviations: BMI=Body Mass Index; EPLC=Placebo group for Estrogen alone trial; ERT=E-alone treatment group; HT Arm=hormone therapy randomization arm; LOT-R=Life Orientation Test- Revised; MET= metabolic equivalent; PERT=Estrogen + Progestin treatment group; PPLC=Placebo group for the Estrogen + Progestin trial; SD=standard deviation

Table 1b.

Characteristics of Participants by Quartile of Optimism Subscale Score (n=7309)

	Quartile of Optimism Subscore				
Variable	**1 (Lowest)**	**2**	**3**	**4 (Highest)**	**P-Value**
Demographic factors					
Age (mean, SD)	70.47 (3.90)	70.57 (3.78)	70.58 (3.87)	70.30 (3.82)	0.1772
Race/Ethnicity					<.0001
Black	109 (6.78%)	95 (5.76%)	104 (5.08%)	197 (9.89%)	
Other	115 (7.16%)	104 (6.31%)	108 (5.27%)	98 (4.92%)	
White	1383 (86.1%)	1449 (87.9%)	1837 (89.7%)	1696 (85.2%)	
Education > high school	1050 (65.3%)	1122 (68.2%)	1463 (71.5%)	1500 (75.4%)	<.0001
Medical History					
Stroke	32 (1.99%)	29 (1.76%)	27 (1.32%)	34 (1.71%)	0.4517
Cardiovascular Disease	186 (11.5%)	175 (10.6%)	160 (7.80%)	170 (8.53%)	0.0002
Hypertension	837 (51.9%)	843 (51.0%)	995 (48.5%)	965 (48.4%)	0.0774
Diabetes	156 (9.68%)	139 (8.41%)	160 (7.80%)	158 (7.93%)	0.1739
Depression (Burnam; mean, SD)	0.06 (0.16)	0.03 (0.10)	0.02 (0.07)	0.02 (0.07)	<.0001
High Cholesterol	301 (19.0%)	337 (20.6%)	346 (17.0%)	326 (16.6%)	0.0056
BMI (mean, SD)	28.23 (5.73)	28.66 (5.74)	28.43 (5.60)	28.77 (5.75)	0.0238
Health Behaviors					
Smoking					0.0015
Never Smoked	799 (50.1%)	830 (51.1%)	1127 (55.7%)	1081 (55.0%)	
Past Smoker	656 (41.2%)	669 (41.2%)	772 (38.1%)	758 (38.5%)	
Current Smoker	139 (8.72%)	126 (7.75%)	125 (6.18%)	128 (6.51%)	
MET-hours per week from walking	3.83 (5.48)	4.03 (5.33)	4.35 (5.55)	4.54 (6.06)	<.0001
HT Arm					0.1657
EPLC	341 (21.2%)	342 (20.7%)	368 (17.9%)	399 (20.0%)	
ERT	321 (19.9%)	329 (19.9%)	381 (18.6%)	394 (19.8%)	
PERT	470 (29.2%)	467 (28.3%)	640 (31.2%)	606 (30.4%)	
PPLC	480 (29.8%)	514 (31.1%)	663 (32.3%)	594 (29.8%)	
Region of Country					<.0001
Northeast	500 (31.0%)	480 (29.1%)	536 (26.1%)	440 (22.1%)	
South	327 (20.3%)	313 (18.9%)	455 (22.2%)	447 (22.4%)	
Midwest	375 (23.3%)	398 (24.1%)	512 (25.0%)	492 (24.7%)	
West	410 (25.4%)	461 (27.9%)	549 (26.8%)	614 (30.8%)	

Abbreviations: BMI=Body Mass Index; EPLC=Placebo group for Estrogen alone trial; ERT=E-alone treatment group; HT Arm=hormone therapy randomization arm; LOT-R=Life Orientation Test- Revised; MET= metabolic equivalent; PERT=Estrogen + Progestin treatment group; PPLC=Placebo group for the Estrogen + Progestin trial; SD=standard deviation

Table 1c.

Characteristics of Participants by Quartile of Pessimism Subscale Score (n=7347)

	Quartile of Pessimism Subscore				
Variable	**1 (Lowest)**	**2**	**3**	**4 (Highest)**	**P-Value**
Demographic factors					
Age (mean, SD)	70.49 (3.83)	70.31 (3.77)	70.49 (3.94)	70.62 (3.86)	0.1468
Race/Ethnicity					<.0001
Black	130 (6.00%)	99 (5.18%)	92 (7.78%)	182 (8.79%)	
Other	82 (3.79%)	83 (4.34%)	56 (4.74%)	201 (9.71%)	
White	1954 (90.2%)	1731 (90.5%)	1034 (87.5%)	1687 (81.5%)	
Education > high school	1694 (78.2%)	1424 (74.4%)	809 (68.6%)	1233 (59.6%)	<.0001
Medical History					
Stroke	29 (1.34%)	30 (1.57%)	18 (1.52%)	45 (2.16%)	0.1827
Cardiovascular Disease	172 (7.93%)	160 (8.36%)	110 (9.30%)	250 (12.0%)	<.0001
Hypertension	1029 (47.4%)	932 (48.7%)	597 (50.5%)	1095 (52.6%)	0.0053
Diabetes	141 (6.50%)	145 (7.57%)	97 (8.20%)	234 (11.3%)	<.0001
Depression (Burnam; mean, SD)	0.01 (0.06)	0.02 (0.07)	0.03 (0.09)	0.06 (0.16)	<.0001
High Cholesterol	352 (16.4%)	358 (18.9%)	224 (19.2%)	386 (18.8%)	0.0945
BMI (mean, SD)	28.07 (5.40)	28.16 (5.58)	28.88 (6.02)	29.14 (5.89)	<.0001
Health Behaviors					
Smoking					0.0016
Never Smoked	1132 (52.9%)	969 (51.3%)	620 (53.3%)	1128 (55.0%)	
Past Smoker	850 (39.7%)	812 (43.0%)	463 (39.8%)	753 (36.7%)	
Current Smoker	158 (7.38%)	109 (5.77%)	81 (6.96%)	170 (8.29%)	
MET-hours per week from walking	4.45 (5.75)	4.40 (5.64)	4.32 (5.83)	3.75 (5.36)	<.0001
HT Arm					<.0001
EPLC	415 (19.1%)	357 (18.6%)	226 (19.1%)	455 (21.9%)	
ERT	392 (18.1%)	334 (17.4%)	234 (19.8%)	473 (22.7%)	
PERT	692 (31.9%)	595 (31.1%)	335 (28.3%)	571 (27.5%)	
PPLC	670 (30.9%)	629 (32.8%)	388 (32.8%)	581 (27.9%)	
Region of Country					0.0002
Northeast	543 (25.0%)	496 (25.9%)	326 (27.6%)	608 (29.2%)	
South	438 (20.2%)	398 (20.8%)	285 (24.1%)	422 (20.3%)	
Midwest	534 (24.6%)	515 (26.9%)	246 (20.8%)	486 (23.4%)	
West	654 (30.2%)	506 (26.4%)	326 (27.6%)	564 (27.1%)	

Abbreviations: BMI=Body Mass Index; EPLC=Placebo group for Estrogen alone trial; ERT=E-alone treatment group; HT Arm=hormone therapy randomization arm; LOT-R=Life Orientation Test- Revised; MET= metabolic equivalent; PERT=Estrogen + Progestin treatment group; PPLC=Placebo group for the Estrogen + Progestin trial; SD=standard deviation

Table 2.

Results of Cox Regression Models Examining the Associations of Probable Dementia, MCI, and Combined Probable Dementia or MCI with LOT-R total score, Optimism Subscore, and Pessimism Subscore[1]

	Probable Dementia		MCI		Probable Dementia/MCI	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
LOT Score (continuous)	0.97 (0.94, 0.99)	0.0101	0.97 (0.95, 0.99)	0.0064	0.96 (0.94, 0.98)	<.0001
Optimism Subscore	0.97 (0.92, 1.01)	0.1525	1.00 (0.96, 1.04)	0.9970	0.98 (0.94, 1.01)	0.1485
Pessimism Subscore	1.06 (1.02, 1.10)	0.0029	1.08 (1.04, 1.12)	<.0001	1.08 (1.05, 1.11)	<.0001

[1]Models includes age, race, education, depression scores, BMI, MET hours per week from walking, HT arm, region of country, cardiovascular disease, diabetes, history of smoking, hypertension, and high cholesterol.

Abbreviations: LOT-R=Life Orientation Test- Revised; MCI=mild cognitive impairment

Table 3.

Effect Modification Models

	Interaction p-value (LOT-R)			Interaction p-value (Optimism Subscore)			Interaction p-value (Pessimism Subscore)		
	Probable Dementia	**MCI**	**Probable Dementia/MCI**	**Probable Dementia**	**MCI**	**Probable Dementia/MCI**	**Probable Dementia**	**MCI**	**Probable Dementia/MCI**
Race/ Ethnicity	0.60	0.75	0.51	0.45	0.93	0.91	0.41	0.18	0.22
Education	0.55	0.62	0.92	0.85	0.45	0.54	0.45	0.25	0.82

All variables in Table 1 included in model

Abbreviations: LOT-R=Life Orientation Test- Revised; MCI=mild cognitive impairment