Title

The relationship between depressive symptoms and subtypes of mild cognitive impairment in post-menopausal women: Results from the Womens Health Initiative Memory Study.

Journal

International Journal of Geriatric Psychiatry, 37(11)

Authors

Korthauer, Laura
Goveas, Joseph
Rapp, Stephen
et al.

Publication Date

2022-11-01

DOI

10.1002/gps.5817

Peer reviewed

HHS Public Access

Author manuscript

Int J Geriatr Psychiatry. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

Int J Geriatr Psychiatry. 2022 November ; 37(11): . doi:10.1002/gps.5817.

The Relationship between Depressive Symptoms and Subtypes of Mild Cognitive Impairment in Post-Menopausal Women: Results from the Women's Health Initiative Memory Study

Laura E. Korthauer, PhD[1], **Joseph S. Goveas, MD**[2], **Stephen R. Rapp, PhD**[3], **Mark A. Espeland, PhD**[4], **Sally A. Shumaker, PhD**[5], **Katelyn R. Garcia, MS**[6], **Rebecca C. Rossom, MD, MS**[7], **Lorena Garcia, MPH, Dr.PH**[8], **Hilary A. Tindle, MD, MPH**[9], **Elena Salmoirago-Blotcher, PhD**[1], **Sylvia Wassertheil-Smoller, PhD**[10], **Oleg Zaslavsky, PhD, MHA, RN**[11], **Barbara Cochrane, PhD, RN, FAAN, FGSA**[12], **Kaycee M. Sink, MD, MAS**[13], **Kamal Masaki, MD**[14], **Ira Driscoll, PhD**[15]

[1]Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI

[2]Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI

[3]Department of Psychiatry and Behavioral Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina

[4]Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina

[5]Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Winston-Salem, North Carolina

[6]Department of Biostatistics and Data Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina

[7]HealthPartners Institute, Minneapolis, MN

[8]Department of Public Health Sciences, University of California-Davis, Davis, CA

[9]Department of Medicine, University of Pittsburgh, Pittsburgh, PA

[10]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York, NY

[11]Department of Biobehavioral Nursing and Health Informatics, University of Washington, Seattle, WA

Corresponding author: Laura Korthauer, PhD., Physicians Office Building, 110 Lockwood St. Suite 430, Providence, RI 02903, laura_korthauer@brown.edu.

Author Contributions

The authors contributed to this manuscript in the following ways: substantial contributions to conception and design (LEK, JSG, SRR, MAE, ID), acquisition of the data (SRR, MAE, SAS), analysis and interpretation of the data (LEK, SRR, MAE, KRG, ID), drafting the manuscript (LEK), critical revisions to the manuscript (all). All authors gave final approval of this version to be published.

Conflicts of Interest

The authors have no conflicts of interest to declare.

[12]Department of Child, Family, and Population Health Nursing, University of Washington, Seattle, WA

[13]Genentech Inc, South San Francisco, CA

[14]Department of Geriatric Medicine, University of Hawaii, Honolulu, HI

[15]Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI

Abstract

Background: Depressive symptoms are associated with age-related cognitive impairment, but the relative risk of specific subtypes of mild cognitive impairment (MCI) conferred by depressive symptoms is unclear. The purpose of this exploratory study was to determine the longitudinal association between baseline depressive symptoms and incident cases of MCI subtypes (amnestic vs. non-amnestic) and probable dementia (Alzheimer's disease, vascular, mixed) among postmenopausal women.

Methods: Depressive symptoms were assessed at study baseline using an 8-item Burnam algorithm in 7,043 postmenopausal women who participated in the Women's Health Initiative Memory Study (WHIMS) and the WHIMS-Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) extension study. During the median 9.4-year follow-up interval, the presence of MCI and probable dementia was classified by a central adjudication committee. Classification of participants by MCI subtype (amnestic single and multi-domain, non-amnestic single and multi-domain) was done algorithmically based on established criteria using data from annual cognitive testing.

Results: At baseline, 557 women (7.9%) had clinically significant depressive symptoms based on Burnam algorithm cut-point of 0.06. Depressive symptoms at baseline were associated with an increased risk of incident amnestic MCI (hazard ratio [HR] = 1.91, 95% confidence interval [CI] 1.32–2.78, $p<.0001$), but not non-amnestic MCI (HR=1.39, 95% CI 0.91–2.14, $p=.13$) after controlling for demographic factors. This relationship between depressive symptoms and amnestic MCI remained consistent after controlling for lifestyle variables, cardiovascular risk factors, antidepressant use, and history of hormone therapy. There were no significant associations between depressive symptoms and incidence of probable dementia.

Conclusion: Depressive symptoms at baseline among postmenopausal older women are associated with higher incidence of amnestic MCI, suggesting that they may be an independent risk factor or part of the early prodrome of dementia.

Keywords

depression; mild cognitive impairment; MCI subtypes; dementia; Alzheimer's disease

Introduction

Clinically significant depressive symptoms are common in older adulthood. Reported prevalence of major depressive disorder in adults over age 65 ranges from 1% to 5% [1], while an estimated 7% to 49% of older adults have clinically relevant depressive symptoms that do not meet criteria for a depressive disorder [2]. Cross-sectional and longitudinal studies have

found a relationship between depressive symptoms and age-related cognitive impairment, although the causal nature of the relationship continues to be debated. Subclinical and syndromal late-life depression may be considered a prodrome of Alzheimer's disease by some[3,4], while others consider depressive symptoms an independent risk factor for cognitive impairment [5,6].

Many studies exploring the relationship between depressive symptoms and cognitive impairment have used diagnoses of mild cognitive impairment (MCI) or all-cause dementia as primary outcomes. However, MCI and dementia diagnoses represent heterogeneous subtypes with distinct etiological features and cognitive profiles. MCI diagnoses are often divided into two subtypes based on profiles of cognitive performance: amnestic (impairment in memory alone or in addition to other cognitive domains) and non-amnestic (single- and multi-domain but no memory impairment) [7,8]. The most prevalent subtypes of dementia are Alzheimer's disease (AD), affecting 13.9% of Americans, and vascular dementia, with a prevalence of 2.4% [9]. The relationship between MCI subtypes and conversion to dementia is complex, as some patients with MCI show cognitive stability or revert to normal cognition [10]. Amnestic MCI is often considered a prodrome of AD, while non-amnestic MCI may signal higher risk for non-AD dementias [11].

A meta-analysis has shown that late-life depression is associated with increased risk of all-cause dementia, including vascular dementia and AD [12]. This is consistent with evidence that cerebrovascular disease may contribute to the development or perpetuation of depression in later life, known as the "vascular depression" hypothesis [13,14]. Newer evidence also implicates depression in later life as an important risk factor for AD [5,15,16]. Better understanding of the relationship between depressive symptoms and subtypes of MCI may help clarify whether depression is a significant risk factor for prodromal AD versus non-AD dementias and suggest different underlying biological mechanisms. This question is particularly important for women's health, as the prevalence of clinically significant depressive symptoms is twice as high in women as in men [17] and women are at higher risk for AD [18]. The menopause transition is an especially salient factor, as perimenopausal women are at 2.5 times greater risk of depressive symptoms compared to pre-menopause[19]. Risk declines during the postmenopausal state, though late-life depressive symptoms remain common, affect around 25% of women,[20] and are associated with cognitive impairment.[21] In 2016, the International Menopause Society produced recommendations stating that while short-term estrogen therapy may improve affective symptoms during the menopausal transition, findings are inconsistent as to whether hormone therapy improves or has no effect on depressive symptoms in postmenopausal women.[22]

The Women's Health Initiative Hormone Trials (WHI-HT), were two randomized controlled trials evaluating the risks and benefits of hormone therapy (estrogen alone versus placebo and estrogen plus progesterone versus placebo) in healthy postmenopausal women, and also assessed depressive symptoms at baseline. An ancillary study, the WHI Memory Study (WHIMS) began in 1995 and was designed to examine the effects of hormone therapy on incident mild cognitive impairment and dementia in 7,479 WHI-HT participants aged 65 or older. Within WHIMS, MCI and probable dementia were adjudicated by a central panel of experts following standardized criteria. Upon conclusion of the WHIMS observational

extension study in 2008, a subset of women participated in WHIMS-Epidemiology of Cognitive Health Outcommes (WHIMS-ECHO), which included annual cognitive evaluation and central adjudication of MCI and probable dementia; this study ended in 2021.

In the WHIMS, pooled results from the estrogen-alone and estrogen plus progestin trials showed that hormone therapy increased incidence of MCI and dementia, a finding that is possible attributable to timing of hormone therapy in the late postmenopausal period.[23] The prevalence and associated characteristics of amnestic and non-amnestic MCI have been previously characterized in the WHIMS study[24], and an association between elevated depressive symptoms and incident cognitive decline was reported in WHIMS [25]. Neither study, however, explored the relative risk of specific subtypes of MCI conferred by depressive symptoms. In this exploratory study, we sought to examine prospectively whether clinically significant depressive symptoms are differentially associated with subtypes of MCI and dementia in postmenopausal women.

Methods

Participants

WHIMS enrolled 7,479 community-dwelling, postmenopausal women aged 65 to 79 years who did not have a diagnosis of dementia at baseline. The study design, protocol, and primary results have been reported elsewhere [26,27]. The WHIMS intervention periods were 1995 to 2002 for the estrogen+progestin trial, and 1995 through 2004 for the estrogen-alone trial. An observational extension study including 5,835 WHIMS participants continued until 2007. A subset of 2,922 women from WHIMS extension was recruited for the WHIMS-ECHO study in 2008, which included further follow-up of cognitive status through an annual administration of a validated cognitive telephone cognitive assessment [28] and continued central adjudication of MCI and dementia. Study protocols were approved by institutional review boards of all participating sites and the National Institutes of Health. Written informed consent was obtained from all participants.

Of the 7,479 women in WHIMS, 173 participants were diagnosed with MCI or probable dementia within 6 months of study baseline and were excluded from this study. Another 263 were missing study measures and were excluded from analysis. This left 7,043 (95%) women with complete data who were included in the study (see CONSORT diagram, Figure 1).

Key Variables

Depressive Symptoms.—Depressive symptoms were measured at study baseline in 1995 with a self-report instrument consisting of the six-item Center for Epidemiologic Studies Depression Scale CES-D; [29] and two items from the Diagnostic Interview Schedule DIS; [30]. The Burnam algorithm, a logistic regression algorithm originally developed for the Medical Outcomes Study [31] was used to derive a composite score between 0 and 1, with higher scores indicating greater depressive symptomatology. A Burnam cut-point of 0.06 has strong sensitivity for detecting clinically significant depressive symptoms in primary care samples [31].

Mild Cognitive Impairment and Dementia Subtypes.—The WHIMS protocol for detecting MCI and probable dementia has been previously published [26,27]. Briefly, the Modified Mini-Mental State (3MS) examination was administered by centrally trained and certified examiners at 39 study sites to all participants at baseline and annual follow-up visits through 2008 (when the telephone battery was initiated). For women who scored below a prespecified cut-point on the 3MS, the examiner administered the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery and proxy interviews [32] plus a standardized interview to assess for psychiatric disorders. These participants were evaluated by a local physician who had experience diagnosing cognitive impairment including dementia following a standardized protocol. Physicians had the option to order a non-contrast computed tomography (CT) brain scan and/or laboratory blood tests to rule out reversible causes of cognitive dysfunction. Lastly, all the information was transmitted for a review and central adjudication at the WHIMS Coordinating Center, Wake Forest School of Medicine by three specialists who classified participants as having normal cognition, MCI or probable dementia according to standardized diagnostic criteria: Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) for dementia and Petersen criteria for MCI [7].

At the beginning of WHIMS-ECHO in 2008, enrolled participants (N=2,841) received annual cognitive assessments by telephone and the same adjudication process continued. All cognitive assessments were performed by centrally trained and certified examiners. The neuropsychological battery included the modified Telephone Interview for Cognitive Status (TICSm) [33], East Boston Memory Test [34], Category Fluency (Animals) [35], Digit Span-Backward [36], and Oral Trail Making Test [37], plus a sleep questionnaire and the 15-item Geriatric Depression Scale [38]. This battery has been validated for telephone administration and demonstrated to be equivalent to face-to-face administration [28]. The annual cognitive assessment also included administration of the Dementia Questionnaire (DQ), a structured interview of a knowledgeable proxy with questions about the participant's cognitive, behavioral, and medical status [39]. All the data from these annual visits were submitted to central adjudication as described above.

For this analysis, we used the data from participants who were adjudicated as having MCI to algorithmically define an MCI subtype for each participant. MCI classification was based on the following four criteria: 1) objective cognitive deficits, defined as at least one score greater than 1.5 standard deviation units below the mean on CERAD subtests of episodic memory (Word List Delayed Recall or Constructional Praxis Recall), verbal fluency (Category Fluency), language (Boston Naming Test-15 item), visuo-construction (Constructional Praxis), processing speed (Trail Making Test, Part A), and executive functioning (Trail Making Test, Part B); 2) observed cognitive problems, as reported by proxy informant; 3) absence of significant impairment in activities of daily living attributable to cognition; and 4) absence of dementia.

Due to the change in the cognitive measures collected for WHIMS-ECHO, the four criteria to classify participants into MCI subtypes were 1) objective cognitive deficits, defined by at least one test score 1.5 standard deviation units below the mean on a measure of memory (East Boston Memory delayed recall), verbal fluency (Category Fluency), attention (Digit

Span), or executive functioning (Oral Trail Making Test, Part B); 2) observed cognitive problems reported by proxy on DQ (i.e., problems with “memory,” “remembering people’s names,” “recognizing familiar faces,” “finding way about indoors,” “finding way on familiar streets,” “remembering a short list of items”); 3) absence of impairment in activities of daily living attributable to cognition, defined as a response of “no,” “don’t know,” or “not applicable” to questions 14–20 of the DQ (“trouble with household tasks,” “trouble handling money,” “trouble grasping situations or explanations,” “difficulty at work,” “trouble dressing or caring for self, including choosing clothes and tying shoes,” “trouble feeding self, including cutting meat and buttering bread,” “trouble controlling bladder or bowels”; and 4) absence of dementia.

Based on the participants’ individual cognitive test scores outlined above, participants were then placed into one of four MCI subtypes: amnestic single domain (deficit on a memory measure and no other tests), non-amnestic single domain (deficit on a non-memory measure and no memory deficit), amnestic multiple domain (deficit on a memory measure and at least one other domain), and non-amnestic multiple domain (deficit on two or more domains other than memory) [8]. During WHIMS and the WHIMS extension, central adjudication included determination of the most probable etiology of dementia (e.g., AD, Vascular, Mixed); however, this subclassification of dementia ceased in 2008 due to insufficient information (no CT, blood, clinical evaluation). Thus, data regarding dementia subtypes are limited and are presented here as a secondary analysis.

Other Relevant Covariates.—Demographic information, medical history, and lifestyle variables were obtained by clinical measurements and self-report, as described elsewhere[40]. Relevant covariates were selected due to their association with depressive symptomology. These included age, self-reported race/ethnicity (White [Not Hispanic], Black, and “Other or Unknown, which includes Hispanic [2.2%], American Indian/Alaska Native [0.3%], and Asian or Pacific Islander [1.7%] individuals), education, income, marital status (never married, separated or divorced, widowed, currently married), MMSE score, current antidepressant use (yes/no), alcohol use (current, past, never), smoking (current, past, never), body mass index (BMI; weight [kg]/height^2 [m^2]), frequency of exercise (0, <2, 2–3, ≥4 times per week), hypertension treatment (no hypertension, untreated, treated), self-reported history of diabetes, cardiovascular disease, or stroke (yes/no), prior hormone therapy (yes/no), and WHI treatment assignment (whether women were randomized to the intervention arm [estrogen-alone, estrogen+progestin] or the control group [matching placebo] in the respective studies. These covariates were consistent with those used by Goveas and colleagues [25] to permit comparison with their analyses.

Statistical Analyses

Participants were stratified into two groups, presence or absence of clinically significant depressive symptoms, based on their Burnam depression score at enrollment in WHIMS (Burnam algorithm cut-point = .06). Baseline characteristics were compared using chi-square test for categorical variables and general linear models for continuous variables. Cox proportional hazards models were used to evaluate the association between categorical measures of depressive symptoms and incidence of mild cognitive impairment with the

following adjustments: *Model 1*: depressive symptoms, age, race, education, family income, and marital status; *Model 2*: all variables in model 2 as well as lifestyle variables (alcohol, smoking, exercise status) and health variables (antidepressant use, BMI, hypertension, diabetes, CVD, stroke, prior hormone therapy, WHI treatment arm). Separate models were constructed for mild cognitive impairment (MCI), probable dementia (PD), and any cognitive impairment (a composite outcome of first MCI or PD). Proportional hazard assumptions were assessed through graphics and by testing whether there was a significant time-dependent covariate for the Burnam cut-point; assumptions held for all three outcomes. Additionally, separate models were fitted for the four subtypes of incident MCI: single domain amnestic (aMCI-SD), single domain non-amnestic (naMCI-SD), multi domain amnestic (aMCI-MD), and multi domain non amnestic (naMCI-MD), and the three subtypes of probable dementia: Alzheimer's, Vascular, and Mixed. Interaction tests were performed for any significant interactions with age, race, exercise, smoking status, hypertension, BMI, and APOE status. Within the analyses for overall MCI, we additionally performed a test of interaction on amnestic vs. non-amnestic classes of MCI. For those with on-study cognitive impairment, follow-up time was censored at the date of the cognitive testing that triggered its adjudication. For those without on-study MCI or probable dementia, follow-up was censored at the participant's last cognitive assessment. A two-sided p-value <0.05 was considered statistically significant and no adjustments were made for multiple testing.

Results

Of the 7,043 women included in the present analyses, 557 (7.9%) met criteria for clinically significant depressive symptoms based on the Burnam score cut-point at baseline (Table 1). Women with clinically significant depressive symptoms were more likely to be Black; widowed, separated, or divorced; live in the Northeast or South; report lower educational attainment and income; have lower baseline 3MS scores; be currently taking an antidepressant medication; have a history of alcohol use; have current history of smoking; be sedentary; report prior hormone therapy; and have multiple cardiovascular disease risk factors (hypertension, diabetes, cardiovascular disease). Women in the WHI E+P trial were more likely to have depressive symptoms than those in the E-alone trial, regardless of treatment or placebo conditions. Given the long follow-up interval (maximum of 23 years), a large number of observations were censored due to death (N=1,484; 21.1%) or women being lost to follow-up (N=4,149; 58.9%). Of those lost to follow-up, 86% had at least five years of follow-up data included in the present analyses.

During the follow-up interval (median = 9.4 years; IQR = 6.1–15.4; range 0.5 – 23.4), 862 women (12.2%) developed MCI and 848 (12.0%) developed probable dementia. Of the 862 women with MCI, 30 (3.5%) were classified as aMCI-SD, 129 (15.0%) as naMCI-SD, 192 (22.3%) as aMCI-MD, and 101 (11.7%) as naMCI-MD. Of the remaining 410 women, 247 (60.2%) did not fully meet criteria for any MCI subtype (40 did not meet criteria from the original WHIMS study period, 48 did not have observed cognitive problems reported by proxy on the DQ, 132 did not have a cognitive test score <1.5 standard deviations below the mean, and 27 did not meet the absence of impairment in activities of daily living criteria). Another 163 (39.8%) had missing data (incomplete DQ). Of the 848 women with probable dementia, 378 (44.6%) women were evaluated for a probable etiology; 106 (28.0%) were

classified as probable AD, 39 (10.3%) as probable Vascular dementia, 27 (7.1%) as Mixed type dementia, 24 (6.3%) as other dementia etiology, 127 (33.6%) as etiology unknown, and 55 (14.6%) were not reviewed for specific etiology due to not having sufficient information about the case.

Analyses of joint outcomes irrespective of MCI or probable dementia subtype showed that having clinically significant depressive symptoms was associated with higher risk of incident MCI (Model 1: HR=1.51, 95% CI 1.21–1.88, $p<.0001$; Model 2 (fully adjusted): HR=1.39, 95% CI 1.10–1.76, $p=.006$), probable dementia (Model 1: HR=1.47, 95% CI 1.17–1.84, $p=.001$; Model 2: HR=1.45, 95% CI 1.14–1.84, $p=.003$), and any cognitive impairment (Model 1: HR=1.51, 95% CI 1.27–1.79, $p<.0001$; Model 2: HR=1.42, 95% CI 1.18–1.71, $p=.0002$) (Table 2).

Table 3 shows the associations between depressive symptoms and amnestic (combined single and multi-domain) and non-amnestic (combined single and multi-domain) MCI. After adjusting for demographic characteristics (Model 1), depressive symptoms were associated with higher risk of amnestic MCI (HR=1.91, 95% CI 1.32–2.78, $p<.0001$), while there was no significant relationship with non-amnestic MCI (HR=1.39, 95% CI 0.91–2.14, $p=.13$). In the fully adjusted model, the relationship between depression and cognitive impairment persisted for amnestic MCI.

Exploratory analyses examined the association between baseline depressive symptoms and four subtypes of MCI (aMCI-SD, aMCI-MD, naMCI-SD, naMCI-MD) as well as etiology of dementia (Alzheimer's disease, vascular, mixed). Regarding MCI subtypes (Table 4), having clinically significant depressive symptoms at study entry was associated with higher risk of naMCI-SD (HR=1.83, 95% CI=1.08–3.12, $p=.03$) and aMCI-MD (HR=1.88, 95% CI=1.26–2.80, $p=.002$) in Model 1. The effect for naMCI-SD was no longer significant after full adjustment for all relevant covariates including cardiovascular risk factors, WHI treatment assignment, 3MS at baseline, and antidepressant therapy (fully adjusted model: HR=1.51, 95% CI=0.85–2.71, $p=.16$). The effect for aMCI-MD was significant after adjustment for all relevant covariates (HR=1.79, 95% CI 1.16–2.74, $p=.008$). There was no significant association between depressive symptoms and subtypes of incident probable dementia in unadjusted or adjusted models (all p's>.2 in unadjusted models; Table 5).

Tests of interaction were performed for all significant associations described above to determine whether they varied by age, race, cardiovascular risk factors (i.e., exercise, smoking, treatment for hypertension, BMI), or *APOE* genotype. None of these tests of interaction were significant (all p's > .05).

Discussion

Having clinically significant depressive symptoms at baseline was associated with higher risk of incident MCI and probable dementia over a medan follow-up interval of 9.4 years in this cohort of older, post-menopausal women. Analysis of MCI subtypes showed that depressive symptoms were associated with approximately 1.8 times the hazard for developing amnestic MCI, often considered an AD prodrome, after adjusting for potential

confounding variables including prior hormone therapy and WHIMS treatment arm. To our knowledge, this is the first study to investigate the relationship between depressive symptoms and risk of MCI subtypes in a large cohort of post-menopausal women.

Our finding that depressive symptoms were associated with higher risk of incident MCI and probable dementia (independent of subtype) replicates the prior work of Goveas and colleagues[25] in the WHIMS cohort, though with nearly twice the duration of follow-up. The complex relationship between depressive symptoms and incident cognitive impairment has been an active area of research in recent years. Some studies suggest that subclinical and syndromal late-life depression are independent risk factors for AD [5,15,41], while others suggest that depression may be more closely related to vascular dementia [12,42] or just a part of the AD prodrome [16,43], though these hypotheses are not mutually exclusive.

Large prospective studies, such as WHIMS, can help disentangle these relationships. Investigating subtypes of MCI is one method of examining the association between depressive symptomatology and cognitive impairment. Although individual cognitive trajectories vary, the distinction between amnestic and non-amnestic MCI subtypes has diagnostic and prognostic utility. Patients with amnestic MCI show a more precipitous course of cognitive decline than those with non-amnestic MCI[44]. Amnestic MCI is also associated with greater medial temporal lobe atrophy[45], medial temporal lobe hypometabolism [46], and greater beta-amyloid deposition on amyloid PET[47]. There is some controversy over the diagnostic stability and validity of the single- versus multi-domain MCI distinction, as single domain impaired individuals have a high rate of reversion to cognitive normality,[48] and the present study was limited by low case counts for the aMCI-SD subtype. However, longitudinal studies consistently demonstrate that amnestic MCI is associated with a higher risk of progression to Alzheimer's type dementia compared to non-amnestic MCI[49]. Thus, our finding that women with depressive symptoms at baseline are at greater risk for amnestic than non-amnestic MCI suggests that depressive symptoms may be a greater risk factor for Alzheimer's type dementia versus non-Alzheimer's etiologies of cognitive impairment. Our findings are also congruent with the hypothesis that depressive symptoms may emerge as a part of an early neuropsychiatric prodrome of AD [50].

The mechanisms linking depressive symptoms to AD and other causes of age-related cognitive impairment are complex and likely multifactorial. Depressed mood is associated with neuroendocrine changes, including disruption to the hypothalamic-pituitary-adrenal (HPA) axis that causes chronic elevation of adrenal glucocorticoid levels. HPA axis dysregulation with hypercortisolemia may contribute to a variety of pathological processes that increase risk for cognitive decline, including metabolic syndrome, disrupted endothelial functioning, elevated cytokine levels, neuroinflammation, and oxidative stress [51]. Each of these processes has also been linked to risk for AD [52] and elevated glucocorticoid levels have been directly associated with AD neuropathology, both amyloid and tau [53]. Depressed mood may also affect engagement in positive lifestyle behaviors (e.g., exercise, healthy diet) that impact risk of AD [54]. Although the present study cannot disentangle the potential causal mechanisms, our finding of an association between depressive symptoms and amnestic MCI is consistent with evidence linking elevated glucocorticoid levels to downstream effects on medial temporal lobe systems supporting memory through these biological processes [55].

Future studies are needed to elucidate these causal mechanisms and to determine whether treatment of depressive symptoms may reduce progression of AD.

This study is not without limitations. We relied on slightly different operational criteria for determining MCI subtypes for years in which women were in the WHIMS versus WHIMS-ECHO extension study. Different neuropsychological testing batteries were used between these studies, as well. This may have led to differences in the incidence rates of amnestic versus non-amnestic MCI across studies. We were also limited by the low incidence of certain MCI subtypes, particularly aMCI-SD, which limited statistical power. Thus, our analyses breaking amnestic and non-amnestic MCI into single and multi-domain categories should be considered exploratory and used to guide future confirmatory studies. Another limitation was the fact that adjudication of probable dementia etiology (e.g., AD, vascular, mixed) stopped in November of 2008, limiting the number of events within each etiologic category. There was also a large range of follow-up interval (0.5 to 23.4 years) because many observations were censored due to death (21%) or being lost to follow-up (59%), though this weakness is offset by the fact that 86% had at least five years of follow-up data. Another limitation was that self-report measures were used to determine the presence of vascular risk factors and other aspects of medical history, which may have led to inaccurate characterization of these important covariates. Additionally, presence of clinically significant depressive symptoms was based on the Burnam algorithm rather than a gold standard such as a standardized interview. The Burnam screen has a sensitivity of 74% and specificity of 87% for current major depression and dysthymia compared to clinician diagnoses using the Structured Clinical Interview for DSM-IV (SCID), but its positive predictive power is low (20%)[56]. Finally, we were unable to distinguish between women with late-onset depressive symptoms and those with recurrent depression over the life course. The mechanisms underlying late-onset versus recurrent depressive symptoms may be distinct and confer unique risk for Alzheimer's disease versus other causes of cognitive impairment. Replication of findings using structured clinical interviews to establish presence of depressive disorder and more detailed assessment of lifetime depressive symptoms will be an important area for future research. An important strength of this study is the long duration of follow-up in a well-characterized cohort of post-menopausal women.

In summary, we found that among post-menopausal women, having clinically significant depressive symptoms at baseline nearly doubled the risk of developing amnestic MCI over a median 9.4 years of follow-up. This suggests that adequate treatment of late-life depression may be an important aspect of prevention of cognitive impairment in older women.

Acknowledgments

We would like to thank the following WHI investigators:

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg

Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard;

(Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland

Sponsor's Role

The sponsor, the National Institutes of Health, consulted with the 40 clinical centers on the original design of the Women's Health Initiative, which was the cohort that this paper's analysis was based upon. The methods, subject recruitment, and data collections were the collective responsibility of all investigators at the 40 clinical centers and not the sponsor. The data analysis and preparation of the paper was done by the authors of this manuscript. The study sponsor had no role in the analysis, preparation, or views expressed in this paper.

Funding:

This work was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), U.S. Department of Health and Human Services through Contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. Wyeth-Ayerst Research Laboratories, Philadelphia, Pennsylvania supplied the active study drug and placebo. Wyeth Pharmaceuticals funded the WHIMS, in part, as an ancillary study to the WHI. WHIMS-ECHO was funded by the National Institute on Aging, Contract No. HHSN-271-2011-00004C.

References

1. Fiske A, Wetherell JL, Gatz M. Depression in older adults. Annu Rev Clin Psychol. 2009;5:363–89. doi:10.1146/annurev.clinpsy.032408.153621 [PubMed: 19327033]
2. Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. Acta Psychiatr Scand. May 2006;113(5):372–87. doi:10.1111/j.1600-0447.2006.00770.x [PubMed: 16603029]
3. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Arch Gen Psychiatry. May 2012;69(5):493–8. doi:10.1001/archgenpsychiatry.2011.1481 [PubMed: 22566581]
4. Panza F, Frisardi V, Capurso C, et al. Late-life depression, mild cognitive impairment, and dementia: possible continuum? Am J Geriatr Psychiatry. Feb 2010;18(2):98–116. doi:10.1097/JGP.0b013e3181b0fa13 [PubMed: 20104067]
5. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. May 2006;63(5):530–8. doi:10.1001/archpsyc.63.5.530 [PubMed: 16651510]
6. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. Neurology. Jul 2010;75(1):27–34. doi:10.1212/WNL.0b013e3181e62124 [PubMed: 20603482]
7. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. Sep 2004;256(3):183–94. doi:10.1111/j.1365-2796.2004.01388.x [PubMed: 15324362]
8. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. Sep 2004;256(3):240–6. doi:10.1111/j.1365-2796.2004.01380.x [PubMed: 15324367]
9. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29(1–2):125–32. doi:10.1159/000109998 [PubMed: 17975326]
10. Aerts L, Heffernan M, Kochan NA, et al. Effects of MCI subtype and reversion on progression to dementia in a community sample. Neurology. Jun 06 2017;88(23):2225–2232. doi:10.1212/WNL.0000000000004015 [PubMed: 28490651]

11. Michaud TL, Su D, Siahpush M, Murman DL. The Risk of Incident Mild Cognitive Impairment and Progression to Dementia Considering Mild Cognitive Impairment Subtypes. Dement Geriatr Cogn Dis Extra. 2017 Jan-Apr 2017;7(1):15–29. doi:10.1159/000452486 [PubMed: 28413413]
12. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry. May 2013;202(5):329–35. doi:10.1192/bjp.bp.112.118307 [PubMed: 23637108]
13. Sheline YI, Pieper CF, Barch DM, et al. Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. Arch Gen Psychiatry. Mar 2010;67(3):277–85. doi:10.1001/archgenpsychiatry.2009.204 [PubMed: 20194828]
14. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. Arch Gen Psychiatry. Oct 1997;54(10):915–22. [PubMed: 9337771]
15. Kida J, Nemoto K, Ikejima C, et al. Impact of Depressive Symptoms on Conversion from Mild Cognitive Impairment Subtypes to Alzheimer's Disease: A Community-Based Longitudinal Study. J Alzheimers Dis. 2016;51(2):405–15. doi:10.3233/JAD-150603 [PubMed: 26890740]
16. Singh-Manoux A, Dugravot A, Fournier A, et al. Trajectories of Depressive Symptoms Before Diagnosis of Dementia: A 28-Year Follow-up Study. JAMA Psychiatry. 07 01 2017;74(7):712–718. doi:10.1001/jamapsychiatry.2017.0660 [PubMed: 28514478]
17. Sonnenberg CM, Beekman AT, Deeg DJ, van Tilburg W. Sex differences in late-life depression. Acta Psychiatr Scand. Apr 2000;101(4):286–92. [PubMed: 10782548]
18. Laws KR, Irvine K, Gale TM. Sex differences in Alzheimer's disease. Curr Opin Psychiatry. 03 2018;31(2):133–139. doi:10.1097/YCO.0000000000000401 [PubMed: 29324460]
19. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry. Apr 2006;63(4):375–82. doi:10.1001/archpsyc.63.4.375 [PubMed: 16585466]
20. Cheung ESL, Mui AC. Gender Variation and Late-life Depression: Findings from a National Survey in the USA. Ageing Int. Nov 08 2021:1–18. doi:10.1007/s12126-021-09471-5
21. Korten NC, Penninx BW, Kok RM, et al. Heterogeneity of late-life depression: relationship with cognitive functioning. Int Psychogeriatr. Jun 2014;26(6):953–63. doi:10.1017/S1041610214000155 [PubMed: 24565278]
22. Baber RJ, Panay N, Fenton A, Group IW. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. Apr 2016;19(2):109–50. doi:10.3109/13697137.2015.1129166 [PubMed: 26872610]
23. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. Jun 23 2004;291(24):2947–58. doi:10.1001/jama.291.24.2947 [PubMed: 15213206]
24. Rapp SR, Legault C, Henderson VW, et al. Subtypes of mild cognitive impairment in older postmenopausal women: the Women's Health Initiative Memory Study. Alzheimer Dis Assoc Disord. 2010 Jul-Sep 2010;24(3):248–55. doi:10.1097/WAD.0b013e3181d715d5 [PubMed: 20473134]
25. Goveas JS, Espeland MA, Woods NF, Wassertheil-Smoller S, Kotchen JM. Depressive symptoms and incidence of mild cognitive impairment and probable dementia in elderly women: the Women's Health Initiative Memory Study. J Am Geriatr Soc. Jan 2011;59(1):57–66. doi:10.1111/j.1532-5415.2010.03233.x [PubMed: 21226676]
26. Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Control Clin Trials. Dec 1998;19(6):604–21. [PubMed: 9875839]
27. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. May 28 2003;289(20):2651–62. doi:10.1001/jama.289.20.2651 [PubMed: 12771112]

28. Rapp SR, Legault C, Espeland MA, et al. Validation of a cognitive assessment battery administered over the telephone. J Am Geriatr Soc. Sep 2012;60(9):1616–23. doi:10.1111/j.1532-5415.2012.04111.x [PubMed: 22985137]
29. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Applied psychological measurement. 1977;1(3):385–401.
30. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. Arch Gen Psychiatry. Apr 1981;38(4):381–9. doi:10.1001/archpsyc.1981.01780290015001 [PubMed: 6260053]
31. Burnam MA, Wells KB, Leake B, Landsverk J. Development of a brief screening instrument for detecting depressive disorders. Med Care. Aug 1988;26(8):775–89. doi:10.1097/00005650-198808000-00004 [PubMed: 3398606]
32. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. Sep 1989;39(9):1159–65. [PubMed: 2771064]
33. Welsh KA, Breitner JC, Magruder-Habib KM. Detection of dementia in the elderly using telephone screening of cognitive status. Neuropsychiatry, Neuropsychology, & Behavioral Neurology. 1993;
34. Scherr PA, Albert MS, Funkenstein HH, et al. Correlates of cognitive function in an elderly community population. Am J Epidemiol. Nov 1988;128(5):1084–101. doi:10.1093/oxfordjournals.aje.a115051 [PubMed: 3189282]
35. Lezak M, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. Oxford University Press; 2012.
36. Wechsler D WAIS-R manual: Wechsler adult intelligence scale-revised. Psychological Corporation; 1981.
37. Ricker JH, Axelrod BN. Analysis of an Oral Paradigm for the Trail Making Test. Assessment. Mar 1994;1(1):47–52. doi:10.1177/1073191194001001007 [PubMed: 9463499]
38. Yesavage JA, Sheikh JI. Geriatric depression scale (GDS) recent evidence and development of a shorter version. Clinical gerontologist. 1986;5(1–2):165–173.
39. Kawas C, Segal J, Stewart WF, Corrada M, Thal LJ. A validation study of the Dementia Questionnaire. Arch Neurol. Sep 1994;51(9):901–6. doi:10.1001/archneur.1994.00540210073015 [PubMed: 8080390]
40. Group TWsHIS. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials. 1998;19(1):61–109. [PubMed: 9492970]
41. Xu J, Li Q, Qin W, et al. Neurobiological substrates underlying the effect of genomic risk for depression on the conversion of amnestic mild cognitive impairment. Brain. 12 01 2018;141(12):3457–3471. doi:10.1093/brain/awy277 [PubMed: 30445590]
42. Richard E, Reitz C, Honig LH, et al. Late-life depression, mild cognitive impairment, and dementia. JAMA Neurol. Mar 01 2013;70(3):374–82. doi:10.1001/jamaneurol.2013.603
43. Amieva H, Le Goff M, Millet X, et al. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Ann Neurol Nov 2008;64(5):492–8. doi:10.1002/ana.21509 [PubMed: 19067364]
44. Glynn K, O'Callaghan M, Hannigan O, et al. Clinical utility of mild cognitive impairment subtypes and number of impaired cognitive domains at predicting progression to dementia: A 20-year retrospective study. Int J Geriatr Psychiatry. 01 2021;36(1):31–37. doi:10.1002/gps.5385 [PubMed: 32748438]
45. Csukly G, Sirály E, Fodor Z, et al. The Differentiation of Amnestic Type MCI from the Non-Amnestic Types by Structural MRI. Front Aging Neurosci. 2016;8:52. doi:10.3389/fnagi.2016.00052 [PubMed: 27065855]
46. Clerici F, Del Sole A, Chiti A, et al. Differences in hippocampal metabolism between amnestic and non-amnestic MCI subjects: automated FDG-PET image analysis. Q J Nucl Med Mol Imaging. Dec 2009;53(6):646–57. [PubMed: 20016455]
47. Lee SH, Lee JH, Byun MS, et al. Comparison of Amyloid Positivity Rate and Accumulation Pattern between Amnestic and Non-Amnestic Type Mild Cognitive Impairment. Psychiatry Investig. Jun 2020;17(6):603–607. doi:10.30773/pi.2020.0063

48. Han JW, Kim TH, Lee SB, et al. Predictive validity and diagnostic stability of mild cognitive impairment subtypes. Alzheimers Dement. Nov 2012;8(6):553–9. doi:10.1016/j.jalz.2011.08.007 [PubMed: 23102125]

49. Bradfield NI, Ames D. Mild cognitive impairment: narrative review of taxonomies and systematic review of their prediction of incident Alzheimer's disease dementia. BJPsych Bull. Apr 2020;44(2):67–74. doi:10.1192/bjb.2019.77 [PubMed: 31724527]

50. Ismail Z, Gatchel J, Bateman DR, et al. Affective and emotional dysregulation as pre-dementia risk markers: exploring the mild behavioral impairment symptoms of depression, anxiety, irritability, and euphoria. Int Psychogeriatr. 02 2018;30(2):185–196. doi:10.1017/S1041610217001880 [PubMed: 28899446]

51. Pariante CM. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. Eur Neuropsychopharmacol. 06 2017;27(6):554–559. doi:10.1016/j.euroneuro.2017.04.001 [PubMed: 28479211]

52. Shen XN, Niu LD, Wang YJ, et al. Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies. J Neurol Neurosurg Psychiatry. 05 2019;90(5):590–598. doi:10.1136/jnnp-2018-319148 [PubMed: 30630955]

53. Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. J Neurosci. Aug 30 2006;26(35):9047–56. doi:10.1523/JNEUROSCI.2797-06.2006 [PubMed: 16943563]

54. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 08 08 2020;396(10248):413–446. doi:10.1016/S0140-6736(20)30367-6 [PubMed: 32738937]

55. Nguyen DM, Yassa MA, Tustison NJ, et al. The Relationship Between Cumulative Exogenous Corticosteroid Exposure and Volumes of Hippocampal Subfields and Surrounding Structures. J Clin Psychopharmacol. 2019 Nov/Dec 2019;39(6):653–657. doi:10.1097/JCP.0000000000001120 [PubMed: 31688386]

56. Tuunainen A, Langer RD, Klauber MR, Kripke DF. Short version of the CES-D (Burnam screen) for depression in reference to the structured psychiatric interview. Psychiatry Res. Sep 20 2001;103(2–3):261–70. doi:10.1016/s0165-1781(01)00278-5 [PubMed: 11549413]

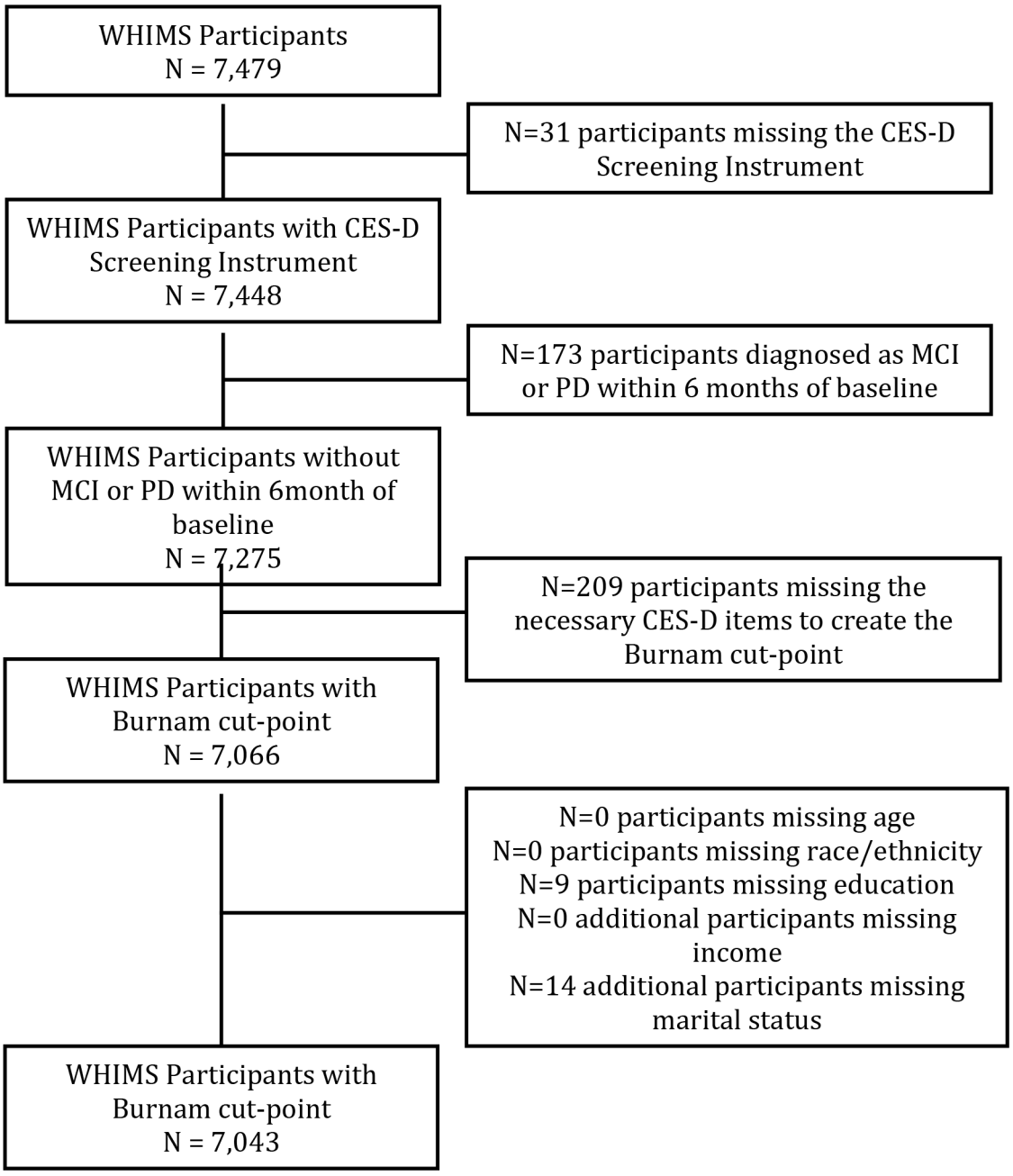

Figure 1.
CONSORT diagram.

Table 1.

Baseline characteristics

Characteristics	Total Sample	Depressive Symptoms	No Depressive Symptoms	P-value
Overall	7043(100)	554 (7.9)	6489 (92.1)	
Age (years)	71.0 ± 0.1	70.9± 0.2	71.0± 0.1	0.561
Race	.	.	.	0.006
White (Not Hispanic)	6172 (87.6)	463 (83.6)	5709 (88.0)	
Black	478 (6.8)	54 (9.8)	424 (6.5)	
Other or Unknown	393 (5.6)	37 (6.7)	359 (5.5)	
Education	.	.	.	<0.001
< High School	516 (7.3)	77 (13.9)	439 (6.8)	
High School	1556 (22.1)	133 (24.0)	1423 (21.9)	
< 4yrs of College	2847 (40.4)	229 (41.3)	2618 (40.4)	
≥ 4yrs of College	2124 (30.2)	115 (20.8)	2009 (31.0)	
Income	.	.	.	<0.001
<35,000	3788 (53.8)	353 (63.7)	3435 (52.9)	
≥50,000	1474 (20.9)	72 (13.0)	1402 (21.6)	
Unreported	410 (5.8)	41 (7.4)	369 (5.7)	
Marital Status	.	.	.	<0.001
Never Married	237 (3.4)	13 (2.4)	224 (3.5)	
Separated or Divorced	867 (12.3)	82 (14.8)	785 (12.1)	
Widowed	2167 (30.8)	225 (40.6)	1942 (29.9)	
Married	3772 (53.5)	234 (42.2)	3538 (54.5)	
MMSE Score	95.3± 0.1	94.31± 0.2	95.4 ± 0.1	<0.001
Current Antidepressant Use	389 (5.5)	93 (16.8)	296 (4.6)	<0.001
Alcohol Use	.	.	.	<0.001
Nondrinker	911 (13.1)	68 (12.4)	843 (13.1)	
Past drinker	1368 (19.6)	147 (26.8)	1221 (19.0)	
Current drinker	4703 (67.4)	334 (60.8)	4369 (67.9)	
Smoking	.	.	.	<0.001
Never	3715 (53.4)	275 (50.6)	3440 (53.7)	
Past Smoker	2757 (39.7)	203 (37.4)	2554 (39.9)	
Current Smoker	479 (6.9)	65 (12.0)	414 (6.5)	
BMI	.	.	.	0.175
<25.0	2045 (29.2)	146 (26.7)	1899 (29.4)	
25.0–29.9	2539 (36.3)	193 (35.3)	2346 (36.3)	
≥30.0	2421 (34.6)	208 (38.0)	2213 (34.3)	
Exercise, times per week	.	.	.	<0.001
0	4076 (58.0)	364 (65.8)	3712 (57.3)	

Characteristics	Total Sample	Depressive Symptoms	No Depressive Symptoms	P-value
<2	347 (4.9)	26 (4.7)	321 (5.0)	
2–3	1127 (16.0)	79 (14.3)	1048 (16.2)	
≥4	1485 (21.1)	84 (15.2)	1401 (21.6)	
Hypertension Treatment	.	.	.	<0.001
Never	4229 (60.7)	286 (52.5)	3943 (61.4)	
Untreated	589 (8.5)	56 (10.3)	533 (8.3)	
Treated	2150 (30.8)	203 (37.3)	1947 (30.3)	
Diabetes Mellitus	578 (8.2)	70 (12.7)	508 (7.8)	<0.001
Cardiovascular Disease	1202 (17.3)	123 (22.7)	1079 (16.8)	<0.001
Stroke	114 (1.6)	6 (1.1)	108 (1.7)	0.298
WHI Treatment Assignment	.	.	.	0.003
Estrogen Alone	.	.	.	.
Intervention - E	1360 (19.3)	128 (23.1)	1232 (19.0)	
Control - E	1400 (19.9)	130 (23.5)	1270 (19.6)	
Estrogen+Progestin	.	.	.	.
Intervention - EP	2108 (29.9)	146 (26.4)	1962 (30.2)	
Control - EP	2175 (30.9)	150 (27.1)	2025 (31.2)	
Prior Hormone Therapy	3218 (45.7)	283 (51.1)	2935 (45.3)	0.002
Region				
Northeast	1890 (26.8)	174 (31.4)	1716 (26.4)	
South	1480 (21.0)	131 (23.7)	1349 (20.8)	
Midwest	1709 (24.3)	104 (18.8)	1605 (24.7)	
West	1964 (27.9)	145 (26.2)	1819 (28.0)	

*N (%) or Mean ± Standard Error

**Chi-Square tests were used for categorical variables, ANOVA was used for continuous variables

Depressive symptoms are defined as having Burnam score ≥0.06

Table 2.

Hazard ratios for the association of depressive symptoms with incidence of cognitive impairment.

	MCI		Probable Dementia (PD)		PD+MCI	
	Events, Hazard Ratio	**P-value**	**Events, Hazard Ratio**	**P-value**	**Events, Hazard Ratio**	**P-value**
Model 1 (N=7043)	861, 1.51 (1.21, 1.88)	<0.001	845, 1.47 (1.17, 1.84)	0.001	1410, 1.51 (1.27, 1.79)	<0.001
Model 2 (N=6722)	819, 1.39 (1.1, 1.76)	0.006	797, 1.45 (1.14, 1.84)	0.003	1333, 1.42 (1.18, 1.71)	<0.001

Model 1: Burnam cut point, age, race, education, family income, marital status

Model 2: Model 1 plus alcohol consumption, smoking status, exercise, antidepressant use, BMI, hypertension, diabetes, CVD, stroke, prior hormone therapy, treatment arm

Table 3.

Hazard ratios for the association of depressive symptoms with amnestic and non-amnestic mild cognitive impairment.

	Amnestic Single/Multiple Domain		Non-amnestic Single/Multiple Domain	
	Events, Hazard Ratio	**P-value**	**Events, Hazard Ratio**	**P-value**
Model 1 (N=7043)	222, 1.91 (1.32, 2.78)	<0.001	229, 1.39 (0.91, 2.14)	0.13
Model 2 (N=6722)	208, 1.81 (1.21, 2.71)	0.004	215, 1.19 (0.74, 1.92)	0.47

Model 1: Burnam cut point, age, race, education, family income, marital status

Model 2: Model 1 plus alcohol consumption, smoking status, exercise, antidepressant use, BMI, hypertension, diabetes, CVD, stroke, prior hormone therapy, treatment arm

Table 4.

Hazard ratios for the association of depressive symptoms with subtypes of mild cognitive impairment.

	aMCI-SD		naMCI-SD		aMCI-MD		naMCI-MD	
	Events, Hazard Ratio	**P-value**	**Events, Hazard Ratio**	**P-value**	**Events, Hazard Ratio**	**P-value**	**Events, Hazard Ratio**	**P-value**
Model 1 (N=7043)	30, 2.16 (0.74, 6.29)	0.16	128, 1.83 (1.08, 3.12)	0.03	192, 1.88 (1.26, 2.80)	0.002	101, 0.93 (0.45, 1.93)	0.85
Model 2 (N=6722)	27, 1.90 (0.54, 6.66)	0.32	122, 1.51 (0.85, 2.71)	0.16	181, 1.79 (1.16, 2.74)	0.008	93, 0.84 (0.36, 1.97)	0.69

Abbreviations: aMCI-SD = Single Domain Amnestic; naMCI-SD = Single Domain Non-Amnestic; aMCI-MD = Multi Domain Amnestic; naMCI-MD = Multi Domain Non-Amnestic

Model 1: Burnam cut point, age, race, education, family income, marital status

Model 2: Model 1 plus alcohol consumption, smoking status, exercise, antidepressant use, BMI, hypertension, diabetes, CVD, stroke, prior hormone therapy, treatment arm

Table 5.

Hazard ratios for the association of depressive symptoms with incidence of subtypes of probable dementia

	Vascular		AD		Mixed Etiology	
	Events, Hazard Ratio	**P-value**	**Events, Hazard Ratio**	**P-value**	**Events, Hazard Ratio**	**P-value**
Model 1 (N=7043)	39, 0.31 (0.04, 2.24)	0.24	104, 0.79 (0.35, 1.82)	0.58	27, 0.94 (0.22, 4.05)	0.94
Model 2 (N=6722)	33, 0.38 (0.05, 2.88)	0.35	100, 0.86 (0.37, 2.00)	0.73	24, 1.16 (0.26, 5.19)	0.85

Model 1: Burnam cut point, age, race, education, family income, marital status

Model 2: Model 1 plus alcohol consumption, smoking status, exercise, antidepressant use, BMI, hypertension, diabetes, CVD, stroke, prior hormone therapy, treatment arm