Cognitive changes during the menopausal transition: a longitudinal study in women with and without HIV

Pauline M. Maki, PhD,[1] Gayle Springer, MLA,[2] Kathryn Anastos, MD,[3] Deborah R. Gustafson, PhD,[4] Kathleen Weber, MS,[5] David Vance, PhD,[6] Derek Dykxhoorn, PhD,[7] Joel Milam, PhD,[8] Adaora A. Adimora, MD,[9] Seble G. Kassaye, MD,[10] Drenna Waldrop, PhD,[11] and Leah. H. Rubin, PhD[2,12]

Abstract

Objective: To assess longitudinal changes in cognitive performance across menopause stages in a sample comprised primarily of low-income women of color, including women with HIV (WWH).

Methods: A total of 443 women (291 WWH; 69% African American; 18% Hispanic; median age = 42 y) from the Women's Interagency HIV Study completed tests of verbal learning and memory, attention/working memory, processing speed, verbal fluency, motor skills, and executive function first at an index premenopausal visit and thereafter once every 2 years for up to six visits (mean follow-up = 5.7 y). General linear-mixed effects regression models were run to estimate associations between menopause stages and cognition, in the overall sample and in WWH. We examined both continuous scores and categorical scores of cognitive impairment (yes/no >1 standard deviation below the mean).

Results: Adjusting for age and relevant covariates, the overall sample and WWH showed longitudinal declines in continuous measures of learning, memory, and attention/working memory domains from the premenopause to the early perimenopause and from the premenopause to the postmenopause, Ps < 0.05 to < 0.001. Effects on those same domains were also evident in categorical scores of cognitive impairment, with the increased odds of impairment ranging from 41% to 215%, Ps < 0.05 to < 0.001. The increase in predicted probability of impairment by menopausal stage (% affected) ranged from 4% to 13%.

Conclusions: Menopause stage was a key determinant of cognition in a sample of low-income women of color, including WWH. Many of these changes reached a clinically significant level of cognitive impairment.

Key Words: Cognition – HIV – Memory – Menopausal transition – Menopause.

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From the [1]Departments of Psychiatry, Psychology and OB/GYN, University of Illinois at Chicago, Chicago, IL; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY; [4]Department of Neurology, SUNY-Downstate Medical Center, Brooklyn, NY; [5]Cook County Health and Hospitals System and Hektoen Institute of Medicine, Chicago, IL; [6]School of Nursing, University of Alabama at Birmingham, Birmingham, AL; [7]Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami, Coral Gables, FL; [8]Institute for Health Promotion and Disease Prevention Research, University of Southern California, Los Angeles, CA; [9]Department of Medicine, University of North Carolina, Chapel Hill, NC; [10]Department of Medicine/ Division of Infectious Diseases, Georgetown University, Washington, DC; [11]University of Miami Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA; and [12]

Department of Neurology and Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD.

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Address correspondence to: Pauline M. Maki, PhD, Department of Psychiatry, University of Illinois at Chicago, 912 S. Wood St., MC 913, Chicago, IL 60612. E-mail: pmaki1@uic.edu

Women show small but significant declines in verbal memory and processing speed as they transition through menopause.[1-3] These changes appear to be independent of the influence of advancing age and menopausal symptoms (eg, depression, anxiety, vasomotor).[4] The strongest evidence supporting the claim that menopause may be a sex-specific risk factor for cognitive dysfunction comes from large-scale longitudinal studies involving prospective neuropsychological test assessments and validated criteria for staging menopause.[1,2] These studies include the Study of Women's Health Across the Nation (SWAN), which followed 2,362 women for 4 years[2] and the Penn Ovarian Aging study (POA) which followed 403 women over 14 years.[1] The duration of these cognitive changes is not fully characterized, though SWAN findings suggest that difficulties in memory and processing may resolve in the postmenopausal period.[2] Consistent findings were reported in a longitudinal study of 2,411 women enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC) whose performance on tests of verbal learning, verbal memory, and processing speed declined before the final menstrual period (FMP), the onset of the postmenopause.[3] Cross-sectional investigations of the association between menopause stage and cognition have examined a broader range of cognitive abilities, but the findings from these studies are inconsistent.[5-7] Additional longitudinal studies are needed to increase the breadth of cognitive domains assessed and to better elucidate the time course of these changes across the different stages of menopause.

The demonstration that cognitive performance declines across the menopausal transition has increased clinical relevance to women who may be more susceptible to cognitive dysfunction, such as women with HIV (WWH). In these women, menopausal status could compound pre-existing HIV-related cognitive difficulties. Although the incidence of HIV-related dementia has decreased substantially since the introduction of antiretroviral therapy (ART), milder forms of cognitive dysfunction may persist.[8] For example, in the Women's Interagency HIV Study (WIHS), the largest cohort study of the natural and treated history of WWH ($n = 1{,}521$), WWH performed worse than sociodemographically similar women without HIV on measures of verbal learning, delayed memory, and psychomotor speed and attention, but not executive function, fluency, or motor skills.[9] In addition to neuroinflammation, antiretroviral toxicities, legacy (pretreatment) HIV complications, and HIV persistence in the central nervous system, cognitive function in WWH can be compromised by poverty, low education quality and attainment, substance abuse, mental health symptoms and disorders, high levels of stress, medical comorbidities, and limited access to health care.[10,11] A cross-sectional study of 986 WIHS participants (708 WWH) found that vasomotor symptoms (VMS), depressive, and anxiety symptoms, but not menopause stage, were associated with worse cognitive performance in both WWH and women without HIV.[12] Notably, anxiety symptoms were associated with low verbal learning only in WWH.[12] The possibility that menopause-related factors contribute to cognitive dysfunction in WWH, as well as in low-income women, requires further investigation in a longitudinal design.

In this study, we examined longitudinal changes in neuropsychological test performance across menopause stage in WWH and sociodemographically similar women without HIV. We included 443 WIHS participants who were premenopausal and age 35 years and older (index visit), and who completed up to 6 longitudinal cognitive assessments, each 2 years apart. Staging of menopause followed standard procedures used in the SWAN.[13] We predicted that performance on tests of verbal learning and memory and processing speed would decrease from the premenopausal to perimenopause stage and rebound during postmenopause, and that declines would be evident in the overall sample and in the subset of WWH. These data not only address the need to understand menopause as a potential contributor to cognitive dysfunction in WWH, but also whether findings in the SWAN and POA generalize to a racially diverse sample of low-income women and whether the magnitude of effect reaches the level of cognitive impairment that is considered clinically significant.

METHODS

Participants

All participants were enrolled in the WIHS, a longitudinal, multisite cohort study of the natural and treated history of WWH and women without HIV (http://wihshealth.org). Study enrollment occurred initially in October 1994 to November 1995, October 2001 to September 2002 at six study sites (Brooklyn, Bronx, Chicago, DC, Los Angeles, and San Francisco), and January 2011 to January 2014 from five sites (Brooklyn, Bronx, Chicago, DC, and San Francisco). Another wave of enrollment occurred at study sites in the southern US (Chapel Hill, Atlanta, Miami, Birmingham, and Jackson) between October 2013 and September 2015, with outreach to surrounding communities at some sites. Detailed information regarding recruitment procedures and eligibility criteria have been previous published.[14-16] Participants were included in the analysis if they were active on or after October 1, 2008 (first administration of menopause questionnaire), completed two or more visits in this time period, and were age 35 or older ($n = 1{,}331$). Participants were excluded ($N = 520$) from the analysis if they did not complete at least one neuropsychological assessment while premenopausal. After excluding 368 participants who did not have at least one neuropsychological assessment in the peri- or postmenopausal stages, an overall sample of 443 remained for analysis.

Menopause stage

Menopause stage was assessed during an in-person interview and classified according to definitions used in the SWAN, allowing us to compare our findings with those from the SWAN. The SWAN criteria are very similar to criteria established in the Stages of Reproductive Aging Workshop (STRAW) consensus statement,[17] later revised.[18] The SWAN

definitions are as follows: premenopausal (menses in the past 3 mo with no changes in regularity); early perimenopausal (menses in the past 3 mo with change in regularity); late perimenopausal (no menses within the past 3 mo but some menstrual bleeding within the past 12 mo); and postmenopausal (no menses within the past 12 mo).

Neuropsychological test battery

The neuropsychological test battery included the Hopkins Verbal Learning Test-Revised (HVLT-R), Letter-Number Sequencing (LNS), Trail Making (TMT), Stroop Test, Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT), Category Fluency Test (Animals), and Grooved Pegboard. Tests assessed the following seven domains: 1) attention/working memory (outcomes = total correct on LNS control and experimental conditions); 2) executive function (outcomes = time to completion on TMT Part B and Stroop color-word [interference] trial); 3) processing speed (outcomes = total correct on SDMT, time to completion on Stroop word-reading trial); 4) memory (outcome = HVLT-R delayed recall); 5) learning (outcome = total learning across HVLT-R trials); 6) fluency (outcomes = total correct on COWAT and animal tasks); and 7) fine motor skills (outcomes = total time to completion for each hand on grooved pegboard).

All timed outcomes were log transformed to normalize distributions and reverse scored so higher scores represented better performance. For both HIV serostatus groups, continuous T-scores adjusted for age, education, race, and WRAT-R reading scores were then derived for each outcome based on the scores of women without HIV using established procedures.[9,19] Continuous T-scores were used to create domain scores, which served as the primary continuous outcome.[19] The primary categorical outcome was a binary yes/no determination of cognitive impairment (T-score < 40; equivalent to more than one standard deviation below the mean) or no cognitive impairment (T-score ≥ 40). This categorical outcome was determined from a standard of normal performance based on WIHS participants without HIV as in previous WIHS studies.[19] These scores were also adjusted for age, education, race, and WRAT-R reading scores.

Covariates

The covariates of interest were selected based on prior knowledge of factors related to menopause and cognitive function in WIHS studies and were updated at core visits.[12,19,20,21] These covariates included age (years); annual household income ($\leq$\$12,000 per year); current tobacco smoking status (yes vs no); heavy alcohol use in the past 6 months ($>$ 7 drinks/wk or more than 4 drinks in one sitting vs less frequent use); marijuana (yes vs no); and crack, cocaine, and/or heroin use (yes vs no) in the past 6 months; HIV status, Hepatitis C antibody positive (yes vs no); menopausal hormone therapy (recent, former only, or never); oral contraceptive use (recent, former only, or never); and surgical menopause (hysterectomy or bilateral oophorectomy). In analyses restricted to WWH we also assessed current HIV RNA copies per mL of plasma, defined as undetectable ($<$48 copies/mL = yes; $\geq$ 48 = no) based on the Cobas TaqMan HIV-1 ver. 1.0 (CTM v.1.0) assay for 2008-2012 (Roche Molecular Systems, Branchburg, NJ), sensitive to 48 copies HIV RNA/mL or the COBAS Ampliprep/COBAS TaqMan v2.0 HIV-1 assay (Taqman v2.0) for 2012-2018, sensitive to 20 copies HIV RNA/mL (Roche Molecular Systems, Branchburg, NJ). Other HIV clinical variables included history of prior AIDS-defining illness, nadir log CD4+ count (cells per mm^3) and current log CD4+ count, years on cART, and current cART use/adherence (no cART, $<$95% adherent with prescribed cART dosing, or $\geq$ 95% adherent to cART).

Statistical analyses

A series of general linear-mixed effects regression models were used to estimate unadjusted and adjusted associations between menopause transitions and neuropsychological test performance, with a random intercept for study site in the total sample. Menopausal transitions were classified as switching from premenopause to one of three later menopause stages: early perimenopause, late perimenopause, or postmenopause. In models examining the association between menopausal transitions and continuous cognitive scores, the beta coefficients provided estimates of the mean change from the premenopause stage. For categorical measures of cognitive impairment (T score $\leq$ 40), odds ratios (OR) and 95% confidence intervals (CI) were used to determine if the change from premenopause to another menopause stage increased the odds of cognitive impairment. The first set of models adjusted only for age. Subsequent models adjusted for age, household income, hepatitis C virus antibody status, smoking status, heavy alcohol, marijuana, crack, cocaine, and/or heroin use, menopausal hormone therapy, oral contraceptive use, parity, and surgical menopause. In models including WWH only, additional adjustments were made for history of prior AIDS-defining illness, current HIV RNA copies per mL of plasma, nadir log CD4+ count and current log CD4+ count, years on ART/cART, and current cART use, and adherence. The SAS statistical software package, version 9.4 (SAS Institute, Cary, NC) was used for all analyses. All statistical tests were two-tailed with $P < 0.05$ considered as significant.

RESULTS

Population characteristics

The median age of the overall sample at index visit was 42 years (interquartile range [IQR], 38, 46). Most women were non-Hispanic Black (69%), and 18% were Hispanic. The median years of education was 12 (IQR 11,14), and 45% had annual household incomes less than \$12,000. Table 1 provides sociodemographic, behavioral, and clinical characteristics for the total sample and for WWH. Among the WWH, 64% were on cART and 55% had undetectable viral loads ($<$48 copies/mL) at index visit. The average length of follow-up was 5.8 years for the entire sample (5.83 y among WWH), corresponding to an average of 3.8 assessments (range 2-6

TABLE 1. *Participant characteristics in the total sample and among women with HIV (WWH) at the premenopausal visit (''index visit'')*

	Total sample ($n = 443$) *N* (%)	WWH ($n = 291$) *N* (%)
Age, median (IQR), y	42 (38, 46)	42 (39, 46)
HIV status	291 (66)	-
Race		
Non-Hispanic, Black	306 (69)	207 (71)
Non-Hispanic, White	34 (8)	27 (9)
Hispanic	78 (18)	42 (15)
Other	24 (5)	15 (5)
Menopause stages reached through follow-up		
Stayed in premenopause	0 (0)	0 (0)
Early perimenopause	308 (70)	203 (70)
Late perimenopause	104 (23)	61 (21)
Postmenopause	156 (35)	104 (36)
Education, median (IQR), y	12 (11, 14)	12 (11, 14)
WRAT, median (IQR)	93 (93, 105)	93 (79, 105)
Average household income, $\leq$ 12,000	200 (45)	127 (44)
Heavy drinking	78 (18)	44 (15)
HCV antibody positive	44 (10)	30 (10)
Current smoker	187 (42)	109 (37)
Recent marijuana use	87 (20)	49 (17)
Recent crack, cocaine, &/or heroin use	33 (7)	17 (6)
Menopausal symptoms[a]		
CES-D $\geq$ 16	103 (30)	65 (28)
Anxiety		
Irritability, grouchiness	64 (18)	38 (16)
Tense, nervous	40 (11)	29 (12)
Vasomotor symptoms	44 (12)	33 (14)
Sleep disturbances	124 (35)	81 (34)
CD4 count, median (IQR)		
Current	-	636 (410, 938)
Nadir	-	307 (204, 423)
HIV RNA, median (IQR)	-	48 (48, 1233)
HIV RNA undetectable	-	159 (55)
On cART	-	185 (64)
Years on cART, median (IQR)		5.0 (12.2)

cART, combination antiretroviral therapy; CES-D, Center for Epidemiological Studies Depression Scale; HCV, Hepatitis C; IQR, interquartile range; Recent, since last Women's Interagency HIV Study visit; WRAT, Wide Range Achievement Test, reading subtest, scaled score.
[a]Menopause symptoms are those symptom occurring $\geq$ 6 d in the past 2 wk; these data are available for 352 women (235 WWH). Vasomotor symptoms include hot flashes, cold sweats, and night sweats; sleep disturbances include trouble falling asleep, waking up several times during the night, or waking up early. HIV RNA lower limit of detection is 48 copies/mL.

assessments). Participants could transition from the premenopause stage to one or more subsequent stages; overall 70% transitioned from pre- to early perimenopause; 21% transitioned to late perimenopause; and 36% transitioned to postmenopause.

Menopause stage

In analyses adjusting for age and other key covariates in the total sample, performance on tests of learning, memory, and attention/working memory declined from premenopausal to one or more later menopause stages, with no decrease in executive function, fluency, motor function, or processing speed. Below we describe the pattern of change in continuous scores and categorical (cognitive impairment) scores for the total sample and WWH separately.

Continuous cognitive scores

Table 2 shows the results for continuous scores for the total sample adjusted first only for age (which is significantly confounded with advancing menopause stage), and then for age and other covariates, including HIV status. Generally, those findings that were significant in analyses adjusting only age were not only significant but also stronger in analyses adjusting for the full range of covariates, including HIV status. Women showed significant declines in their level of performance in the domains of learning, memory, and attention/working memory in the transition from pre- to early perimenopause ($P < 0.05$ to $P < 0.001$) and in the transition from pre- to postmenopause ($P < 0.01$ to $P < 0.001$). Except for learning ($P < 0.05$), performance did not decline in the transition from pre- to late perimenopause. Together these data indicate that overall declines in learning are sustained through the entire transition, whereas declines in memory and attention/working memory were limited in the transition from pre- to the early perimenopause and postmenopause.

Table 3 shows the changes in continuous scores for the WWH from premenopause to later menopause stages. Similar to the overall sample, WWH showed highly significant declines in learning and memory ($P < 0.001$), and significant but milder declines in attention/working memory ($P < 0.05$)

TABLE 2. *Total sample: estimated change in the unstandardized beta coefficient (B) between the premenopause and later menopause stages*

	Adjusted for chronologic age			Adjusted for chronologic age+ additional factors[a]		
Domain	Pre- to early peri B (SE)	Pre- to late peri B (SE)	Pre- to post B (SE)	Pre- to early peri B (SE)	Pre- to late peri B (SE)	Pre- to post B (SE)
Learning	−1.86 (0.61)[b]	−1.12 (0.99)	−2.46 (0.81)[b]	−1.94 (0.60)[b]	−1.16 (0.98)	−2.72 (0.89)[b]
Memory	−2.07 (0.60)[c]	−1.90 (0.99)[d]	−2.03 (0.81)[e]	−2.11 (0.60)[c]	−1.95 (0.98)[e]	−2.51 (0.88)[b]
Attention/WM	−1.97 (0.58)[c]	−1.59 (0.96)[d]	−3.44 (0.78)[c]	−1.89 (0.58)[b]	−1.52 (0.94)	−3.73 (0.85)[c]
Executive function	−0.76 (0.58)	−0.10 (0.96)	−1.85 (0.78)	−0.89 (0.58)	0.05 (0.95)	−1.06 (0.85)
Psychomotor speed	−0.54 (0.57)	−1.98 (0.94)[e]	−1.39 (0.76)[d]	−0.67 (0.56)	−1.79 (0.92)[d]	−1.35 (0.83)
Fluency	0.74 (0.57)	−0.70 (0.94)	−1.64 (0.76)[e]	−0.91 (0.56)	−0.36 (0.92)	−1.14 (0.83)
Motor	−0.98 (0.61)	−1.27 (0.99)	−0.77 (0.82)	−1.07 (0.59)[d]	−1.43 (0.97)	−1.28 (0.88)

peri, perimenopause; post, postmenopause; Pre, premenopause; WM, working memory.
[a]Additional factors include HIV status, household income, hepatitis C virus antibody status, oral contraceptive use, hormone therapy use, surgical menopause, smoking, heavy alcohol use, marijuana use, and illicit substance use.
[b]$P < 0.01$.
[c]$P < 0.001$.
[d]$P > 0.05$ and $P < 0.10$.
[e]$P < 0.05$.

TABLE 3. *Women with HIV: estimated change in the unstandardized beta coefficient (B) between the premenopause and later menopause stages*

	Adjusted for chronologic age			Adjusted for chronologic age+ additional factors[a]		
Domain	Pre- to early peri B (SE)	Pre- to late peri B (SE)	Pre- to post B (SE)	Pre- to early peri B (SE)	Pre- to late peri B (SE)	Pre- to post B (SE)
Learning	−2.60 (0.72)[b]	−1.67 (1.27)	−2.46 (0.97)[c]	−2.67 (0.71)[b]	−1.13 (1.25)	−2.69 (1.03)[d]
Memory	−3.17 (0.74)[b]	−2.76 (1.30)[c]	−2.08 (0.99)[c]	−3.24 (0.73)[b]	−2.17 (1.28)[e]	−2.59 (1.06)[c]
Attention/WM	−1.65 (0.71)[c]	−0.79 (1.25)	−3.36 (0.94)[b]	−1.53 (0.71)[c]	−0.23 (1.25)	−3.30 (1.02)[d]
Executive function	−1.06 (0.72)	−0.71 (1.28)	−0.80 (0.96)	−1.19 (0.72)[e]	−0.10 (1.26)	−0.97 (1.03)
Psychomotor speed	−0.81 (0.68)	−1.58 (1.21)	−1.94 (0.91)[c]	−0.84 (0.66)	−0.73 (1.16)	−1.74 (0.95)[e]
Fluency	−0.57 (0.73)	−0.54 (1.29)	−1.66 (0.97)[e]	−0.81 (0.71)	0.39 (1.25)	−1.17 (1.02)
Motor	−1.06 (0.75)	−3.28 (1.33)[c]	−0.79 (1.01)	−0.81 (0.74)	−2.75 (1.29)[c]	−0.87 (1.06)

B, unstandardized beta coefficient; peri, perimenopause; post, postmenopause; Pre, premenopause; SE, standard error; WM, working memory.
[a]Additional factors include HIV status, household income, hepatitis C virus antibody status, oral contraceptive use, hormone therapy use, surgical menopause, smoking, heavy alcohol use, marijuana use and illicit substance use, previous AIDS diagnosis, HIV RNA, antiretroviral therapy duration, CD4 (current, nadir), and cART use and adherence.
[b]$P < 0.001$.
[c]$P < 0.05$.
[d]$P < 0.01$.
[e]$P > 0.05$ and $P < 0.10$.

in the transition from pre- to early perimenopause. Scores in all three of these domains (learning, memory, and attention/working memory) also declined from pre- to postmenopause (Ps < 0.05). As in the overall sample, performance did not decline in the transition from pre- to late perimenopause; the exception in WWH was in the domain of motor skills which declined modestly but significantly ($P < 0.05$). These findings in WWH remained significant in analyses controlling for HIV-related clinical factors (Ps < 0.05).

Cognitive impairment scores

Table 4 shows the results for categorical scores (ie, binary yes/no scores indicative of either the presence or absence of cognitive impairment relative to the sample of women without HIV) for the overall sample of women. Generally, findings that were significant in analyses adjusted for age only were also significant in analyses adjusting for the full range of covariates, including HIV. From the pre- to early perimenopause, the odds of impairment in learning, memory, and attention/working memory significantly increased by 60%, 71%, and 41%, respectively (Ps < 0.05). From the pre- to the early perimenopause, the odds of impairment did not increase; the exception was that the odds of impairment in learning increased 94% ($P < 0.01$). From the pre- to postmenopause, the odds of impairment in memory and attention each increased 76% ($P < 0.05$), with a trend for learning.

Table 5 shows the odds of cognitive impairment from the premenopause to later stages among WWH. For memory, there was a ∼2-fold increased odds of impairment (OR = 1.98) during the transition from the pre- to early perimenopause ($P < 0.01$) but no increased odds of memory impairment in any other transition. For learning, there was an increased odds of impairment from premenopause to each of the three later stages. The odds of impairment in learning from the pre- to early perimenopause was 2.1-fold higher ($P < 0.001$), from the pre- to the late perimenopause was 2.6-fold higher ($P < 0.05$), and from the pre- to postmenopause was 76% higher ($P < 0.05$). This pattern indicated that the learning impairment was sustained across the transition, whereas the memory impairment was limited to the early perimenopause. In analyses controlling for HIV-related clinical factors, all of these findings remained except for the

TABLE 4. *Total sample: estimated change in the odds of domain-specific cognitive impairment between the premenopause and later menopause stages*

	Adjusted for chronologic age			Adjusted for chronologic age+ additional factors[a]		
Domain	Pre- to early peri OR (95% CI)	Pre- to late peri OR (95% CI)	Pre- to post OR (95% CI)	Pre- to early peri OR (95% CI)	Pre- to late peri OR (95% CI)	Pre- to post OR (95% CI)
Learning	1.64 (1.21-2.23)[b]	1.36 (0.81-2.26)	1.69 (1.13-2.53)[c]	1.71 (1.24-2.34)[b]	1.35 (0.80-2.28)	1.76 (1.12-2.77)[c]
Memory	1.56 (1.15-2.13)[b]	1.92 (1.19-3.10)[b]	1.52 (1.01-2.30)[c]	1.60 (1.17-2.20)[b]	1.94 (1.19-3.17)[b]	1.51 (0.95-2.40[d]
Attention/WM	1.41 (1.01-1.98)[c]	0.73 (0.38-1.41)	1.67 (1.08-2.58)[c]	1.41 (1.001-1.99)[c]	0.74 (0.38-1.44)	1.76 (1.09-2.85)[c]
Executive function	1.15 (0.83-1.61)	0.88 (0.49-1.58)	1.33 (0.87-2.04)	1.15 (0.82-1.62)	0.89 (0.49-1.61)	1.23 (0.76-2.01)
Psychomotor speed	1.08 (0.77-1.52)	1.42 (0.84-2.39)	1.25 (0.81-1.95)	1.11 (0.78-1.57)	1.41 (0.83-2.39)	1.23 (0.74-2.02)
Fluency	0.92 (0.63-1.33)	0.86 (0.46-1.63)	1.48 (0.94-2.34)[d]	0.93 (0.63-1.36)	0.88 (0.46-1.67)	1.32 (0.78-2.22)
Motor	1.02 (0.80-1.63)	1.20 (0.69-2.09)	0.96 (0.60-1.55)	1.19 (0.82-1.71)	1.24 (0.70-2.20)	1.10 (0.65-1.875)

CI, confidence interval; OR, odds ratio; peri, perimenopause; post, postmenopause; Pre, premenopause; WM, working memory.
[a]Additional factors include HIV status, household income, hepatitis C virus antibody status, oral contraceptive use, hormone therapy use, surgical menopause, smoking, heavy alcohol use, marijuana use and illicit substance use.
[b]$P < 0.01$.
[c]$P < 0.05$.
[d]$P > 0.05$ and $P < 0.10$.

TABLE 5. *Women with HIV: estimated change in the odds of domain-specific cognitive impairment between the premenopause and later menopause stages*

	Adjusted for chronologic age			Adjusted for chronologic age+ additional factors[a]		
Domain	Pre- to early peri OR (95% CI)	Pre- to late peri OR (95% CI)	Pre- to post OR (95% CI)	Pre- to early peri OR (95% CI)	Pre- to late peri OR (95% CI)	Pre- to post OR (95% CI)
Learning	1.93 (1.31-2.84)[b]	1.77 (0.92-3.41)[c]	1.59 (0.94-2.68)[c]	1.98 (1.32-2.98)[b]	1.61 (0.82-3.17)	1.67 (0.94-2.95)[c]
Memory	2.07 (1.41-3.02)[d]	2.49 (1.35-4.58)[b]	1.64 (0.98-2.74)[c]	2.15 (1.45-3.19)[d]	2.26 (1.20-4.25)[e]	1.76 (1.01-3.09)[d]
Attention/WM	1.33 (0.89-2.01)	0.54 (0.22-1.34)	1.53 (0.90-2.59)	1.33 (0.87-2.03)	0.50 (0.20-1.25)	1.59 (0.89-2.84)
Executive function	1.22 (0.81-1.83)	0.92 (0.42-1.99)	1.36 (0.80-2.32)	1.20 (0.78-1.83)	0.83 (0.37-1.82)	1.29 (0.72-2.34)
Psychomotor speed	1.07 (0.69-1.66)	1.05 (0.48-2.30)	1.38 (0.79-2.41)	1.16 (0.73-1.83)	0.99 (0.44-2.21)	1.52 (0.82-2.82)
Fluency	0.84 (0.53-1.34)	0.49 (0.18-1.31)	1.38 (0.80-2.40)	0.99 (0.49-1.34)	1.78 (0.66-4.77)	0.75 (0.22-2.55)
Motor	1.05 (0.68-1.61)	1.53 (0.77-3.02)	0.88 (0.49-1.61)	1.01 (0.65-1.61)	1.37 (0.67-2.79)	1.05 (0.55-2.02)

CI, confidence interval; OR, odds ratio; peri, perimenopause; post, postmenopause; Pre, premenopause; WM, working memory.
[a]Additional factors include HIV status, household income, hepatitis C virus antibody status, oral contraceptive use, hormone therapy use, surgical menopause, smoking, heavy alcohol use, marijuana use, and illicit substance use.
[b]$P < 0.01$.
[c]$P > 0.05$ and $P < 0.10$.
[d]$P < 0.001$.
[e]$P < 0.05$.

increased learning impairment from pre- to postmenopause (data not shown).

To determine the percentage of women affected in the domains of learning, memory, and attention/working memory, we estimated the predicted probability of impairment from the full model for the overall sample of women and for WWH. As these were derived from the full model, they were already adjusted for age and other covariates in that model. Figure 1 shows these results. It is notable that as many as 32% of women met criteria for impairment in at least one cognitive domain during the transition. The mean predicted probability of learning impairment in the pre-, early peri-, and postmenopause was 0.15 (SE = 0.06), 0.23 (SE = 0.08), 0.23 (SE = 0.08), respectively, for the total sample of women and 0.12 (SE = 0.06), 0.23 (SE = 0.11), and 0.21 (SE = 0.10), respectively for WWH. This corresponds to an increase in the probability of learning impairment of 8% to 11% with advancing menopause stage. The mean predicted probability of memory impairment in the pre-, early peri, and postmenopause was 0.21 (SE = 0.06), 0.32 (SE = 0.09), 0.32 (SE = 0.09), respectively, for the overall sample of women and 0.18 (SE = 0.09), 0.31 (SE = 0.12), and 0.29 (0.12), respectively, for WWH. This corresponds to an increase in the probability of memory impairment of 11% to 13% with advancing menopause stage. The mean predicted probability of impairment in attention/working memory in the pre-, early peri, and postmenopause was 0.09 (SE = 0.04), 0.14 (SE = 0.06), 0.16 (SE = 0.06), respectively, for the overall sample of women and 0.08 (SE = 0.05), 0.12 (SE = 0.07), and 0.13 (0.07), respectively, for WWH. This corresponds to an increase in the probability of impairment in attention/working memory of 4% to 7% with advancing menopause stage.

DISCUSSION

In a longitudinal study of 443 women (291 WWH, 66%) over an average follow-up of 5.8 years, cognitive performance declined from the premenopause to later menopause stages—independent of age and other key factors. These declines were

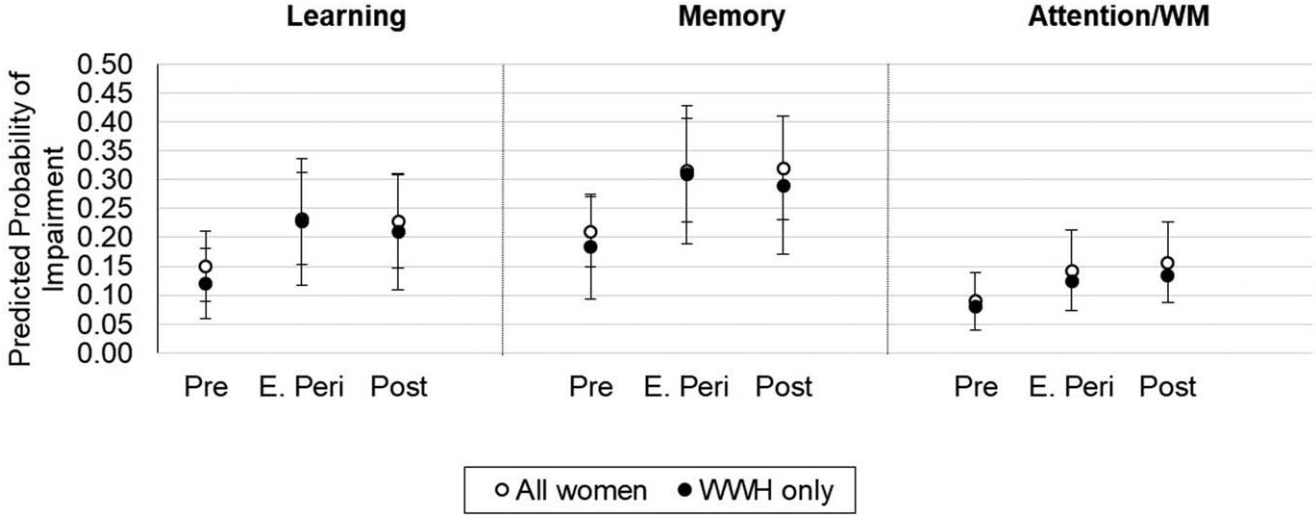

FIG. 1. Predicted probability of impairment in learning, memory, and attention/working memory by menopause stage for the total sample and women with HIV (WWH). E Peri, early perimenopause; Post, postmenopause; Pre, premenopause; WM, working memory; WWH, women with HIV.

primarily evident in three cognitive domains— learning, memory, and attention/working memory. No menopause-related declines were evident in executive function, fluency, or processing speed. To compare findings with prior studies, we analyzed continuous cognitive scores, which reflect the estimate levels of performance that can be in the normal or impaired range of cognitive function. We also analyzed categorical scores of cognitive impairment, which constitute a clinically significant decline. Results from both continuous and categorical scores indicated that most declines were observed in the transition from the pre- to early perimenopause and from the pre- to postmenopause, with few changes in the pre- to late perimenopause. Overall, the data suggest that the menopausal transition is associated with clinically significant declines in cognitive performance in a sample comprised primarily of low-income women of color, including in WWH.

Verbal learning and memory were key outcomes given prior work in SWAN, POA, and ALSPAC showing significant but small changes in those domains from the pre- to perimenopause[1-3] as well as prior work in premenopausal women showing that performance in those domains declines following oophorectomy and rebounds with estrogen therapy.[22] In the overall sample, women showed decreases in learning and memory scores from the pre- to early perimenopause, and the odds of cognitive impairment in those domains were also increased in that transition (60%, and 71% increased odds, respectively). In the overall sample, women also showed decreases in learning and memory from the pre- to postmenopause; the odds of impairment were increased 76% while the odds of a learning impairment were a trend ($P < 0.10$). WWH showed similar declines in these two cognitive outcomes from the pre- to early perimenopause, and from the pre- to the post-menopause, though results for memory impairment in the pre- to post-menopause showed only a trend that did not reach statistical significance and the increase in learning impairment from pre- to postmenopause was no longer significant after controlling for HIV clinical factors. The percentage of women showing significant menopause-related declines in learning and memory was notable. The predicted probability of learning impairment overall increased by 8%, from 15% in the premenopause to 23% in the perimenopause, and remaining at 23% in the postmenopause. The predicted probability of memory impairment overall increased by 11%, from 21% in the premenopause to 32% in the perimenopause, and remaining at 32% in the postmenopause. For WWH, this increase in memory impairment was also striking, increasing by 13% from the premenopause to early perimenopause. Thus, while the majority of women did not experience a clinically significant menopause-related decline in learning and memory, a subset of women showed a cognitive vulnerability.

This study revealed novel findings of menopause-related declines in the domain of attention/working memory, domains that have received limited evaluation in prior studies. The pattern of decline in attention generally mirrored that of learning and memory, with declines evident in the pre- to early perimenopause and the pre- to postmenopause. For continuous scores, this pattern was seen in the overall sample and in WWH. For categorical scores, declines in attention/working memory were seen only in the overall sample and not in analyses restricted to WWH. Thus, WWH show declines in this domain in the normal range of performance across the menopause transition relative to women without HIV, but these declines do not reach the level of cognitive impairment. This pattern suggests that for WWH menopause-related impairment in cognitive function is more evident in learning and memory than for attention. This is consistent with the pattern for women in this cohort, as the odds of impairment in attention just reached statistical significance (OR = 1.41, 95% CI = 1.001-1.99). Of the POA, SWAN, and ALSPAC studies, SWAN and ALSPAC measured attention/working memory and neither found menopause-related changes in that domain as measured by the Digit Span Backward test.[2] Like the current study, the cross-sectional Rochester Investigation of Cognition Across Menopause (RICAM) measured attention/working memory with the LNS and found impairments in the early postmenopause.[6] In contrast to RICAM findings, in the present study attention also declined in the transition to the early perimenopause. Further, RICAM assessed attention in the first year postmenopause and results here extend later into the postmenopause. Overall, our results suggest a decline in attention/working memory that does not reach the level of clinical impairment but that continues into postmenopause. It should be noted that changes in attention/working memory even in the normal range can affect daily function. For example, prior work has shown that scores on tests of working memory and attention are strong predictors of subjective cognitive complaints in people with HIV and midlife women.[23-25]

We previously hypothesized that menopause-related changes might contribute to sex differences in cognitive performance in people with HIV after controlling for sociodemographic, behavioral, and clinical factors. The initial longitudinal study of WWH from the WIHS showed that HIV-associated declines in cognition were most evident in the domain of delayed memory, a pattern that differed from that typically seen in men with HIV.[9] The current findings suggest that menopause stage affects memory for verbal material. In our previous work, WWH showed worse cognitive performance than men with HIV (MWH) in processing speed, psychomotor speed, executive function, and motor skills; learning and memory could not be assessed in that study because different tests were used in men versus women.[20] Given that no menopause stage effects were evident in psychomotor speed or executive function in the present study, it appears unlikely that menopause accounts for those sex differences. Future longitudinal studies are needed to determine whether MWH and WWH differ in verbal learning and memory, domains that showed an effect of menopause stage.

Our study had notable strengths and weaknesses. The overall sample size (total $n = 443$) was substantial with WWH ($n = 291$) and women without HIV ($n = 152$). The

longitudinal design was a strength, as previous cross-sectional analyses of WIHS data found no significant differences in cognitive performance by menopause stage.[12] Longitudinal studies are particularly important in cohorts such as the WIHS where participants have multiple health comorbidities and varying additional risk factors for cognitive dysfunction. The frequency of testing once every 2 years likely limited our ability to detect longitudinal changes in the late perimenopause, which is the shortest stage estimating to last, on average, 1 to 3 years.[18] Indeed only 23% of our cohort ($n = 104$) were tested in that stage and may have contributed to the lack of findings in that stage. About half of the sample was followed through to the postmenopause stage, so we may have limited power to detect small effect sizes. Nevertheless, we were able to detect cognitive changes from pre- to early perimenopause and pre- to postmenopause in the domains of learning, memory, and attention/working memory. Our prior primary outcomes were learning, memory, and processing speed. While we used composite scores to limit the number of comparisons, we did not control for multiple comparisons when examining other domains, including attention/working memory. The gold-standard criteria for determining menopause stage rely on menstrual cycle characteristics, but menstrual cycle irregularities of WWH and women with a history of substance use are well recognized,[26] and may have led to misclassification of menopause stage. Frequent amenorrhea in WWH[26] might also account for the lack of findings in the late perimenopause when compared with HIV-infected women. Nevertheless stage-related changes in the early perimenopause and postmenopause were detectable in WWH and were similar to those of women without HIV. Lastly, cognitive impairment was determined based on a referent sample of low-income WIHS participants without HIV. This approach has an advantage when the goal is to determine the effects of menopause separate from other factors influencing cognitive function in this sample such as HIV, poverty, education, substance use history, and mental health factors. Conversely, this approach likely underestimates rates and severity of cognitive impairment based on the general population of midlife women in the United States.

CONCLUSION

Overall, these findings indicate that menopause stage is an important determinant of cognitive performance in a sample of low-income women of color, including WWH. A novel finding was that clinically significant cognitive declines, which we classified as cognitive impairment, persisted in the postmenopause for learning and memory; subtler declines in attention continued into the postmenopause. These findings in the postmenopause differ with findings from SWAN and POA, large longitudinal studies of racially and ethnically diverse but higher income women without HIV. This difference raises the possibility that lower income women with multiple risk factors for cognitive dysfunction including low education, mental health disorders, high-trauma exposure, substance use, and infectious disease like HCV and HIV may be more vulnerable to longer-lasting cognitive effects of menopause. It will be important in future studies to identify which factors account for individual differences in cognitive declines associated with the menopause.

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