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The KEEPS-Cognitive and Affective Study: Baseline Associations between Vascular Risk Factors and Cognition

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Abstract. Midlife vascular risk factors influence later cognitive decline and Alzheimer's disease (AD). The decrease in serum estradiol levels during menopause has been associated with cognitive impairment and increased vascular risk, such as high blood pressure (BP), which independently contributes to cognitive dysfunction and AD. We describe the extent to which vascular

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risk factors relate to cognition in healthy, middle-aged, recently postmenopausal women enrolled in the Kronos Early Estrogen Prevention Cognitive and Affective Study (KEEPS-Cog) at baseline. KEEPS-Cog is a double-blind, randomized, placebo-controlled, parallel group, clinical trial, investigating the efficacy of low-dose, transdermal 17β-estradiol and oral conjugated equine estrogen on cognition. All results are cross-sectional and represent baseline data only. Analyses confirm that the KEEPS-Cog cohort ($n = 571$) was middle aged (mean 52.7 years, range 42–59 years), healthy, and free of cognitive dysfunction. Higher systolic BP was weakly related to poorer performance in auditory working memory and attention ($p = 0.004$; adjusted for multiple comparisons $p = 0.10$). This relationship was not associated with endogenous hormone levels, and systolic BP was not related to any other cognitive domain. BP levels may be more sensitive than other vascular risk factors in detecting subtle differences in cognitive task performance in healthy, recently menopausal women. Lower BP early in menopause may affect cognitive domains known to be associated with AD.

Keywords: Attention, blood pressure, clinical trial, cognition, estradiol, estrogen, hormone therapy, memory, vascular risk

INTRODUCTION

Declining serum estrogen levels during the menopausal transition have been linked to increased vascular risk factors and subtle cognitive decline [1, 2]. Results from basic science, observational studies, and clinical trials suggest that hormone therapy (HT) administered soon after menopause may reduce these deleterious vascular and cognitive effects [3, 4]. Specifically, the salutary vascular effects of HT include protection of arterial wall function and lowering blood pressure (BP) [5]. HT administration may also have beneficial cognitive effects, both via direct actions on estrogen receptors in the brain, and indirectly, through HT's beneficial effects on the vasculature.

Increases in vascular risk factors, including hypertension during midlife are associated with an increased risk of Alzheimer's disease (AD) in later life [6]. Similarly, controlled vascular risk factors such as reductions in BP are associated with protection against AD [7–9]. This indicates that long-standing uncontrolled BP and other vascular risk factors may contribute to AD pathology, possibly through decreased cerebral blood flow (CBF) and accumulation of amyloid-β (Aβ), a key pathological feature of AD [10, 11]. Some studies show that the precipitous decrease in serum estradiol levels during the menopausal transition is associated with some cognitive impairment, particularly in attention and memory [12]. Moreover, the decline estradiol increases the risk of hypertension and hypercholesterolemia, factors that independently contribute to cognitive dysfunction and AD [13].

While there is a clear relationship between cognition and clinically diagnosable hypertension, the point at which vascular risk factors influence cognitive task performance is less understood. Moreover, while the menopausal decline in estradiol has been linked to subtle reductions in cognition and increased vascular risk factors, the extent to which estradiol levels influence vascular risk factors and cognition independently or in tandem is unclear.

The majority of research linking vascular factors and cognition has been conducted in older or populations and in samples with established vascular disease [14]. Also, studies have shown that vascular risk factors can influence cognitive task performance in younger populations, whose vascular disease risk factors are within clinically 'normal' limits [15]. For instance, our group [16] and others [17] have reported a relationship between cognitive task performance and BP extending into the normotensive range (i.e., around 120/80 mmHg) in younger samples of healthy men and women (i.e., 18–25 years). These changes in cognition are similar to changes observed in older populations [18].

The Kronos Early Estrogen Prevention Cognitive and Affective Study (KEEPS-Cog) is a 4-year, randomized, double-blind, placebo-controlled, parallel group, clinical trial, designed to investigate the differential efficacy of low-dose estrogen formulations on cognition in recently postmenopausal women. The comprehensive baseline data from the KEEPS-Cog provides an excellent resource to investigate the relationship among vascular risk factors, cognitive task performance and endogenous sex hormone levels in healthy, recently postmenopausal women.

The purpose of this study was to define the relationships among vascular risk factors and cognitive task performance in healthy, middle-aged, recently postmenopausal women enrolled in the KEEPS-Cog study prior to randomization to study medication. Additionally, we sought to explore the extent to which this

relationship might be associated with serum endogenous sex hormone levels.

METHODS

The KEEPS-cog is a sub-study of the Kronos Early Estrogen Prevention Study (KEEPS). Details of the trial design, exclusion criteria, treatment assignment, and participant characteristics have been published previously [19, 20]. The University of Wisconsin in Madison was the coordinating site for the KEEPS-Cog trial. The trial consisted of four visits over four years (baseline prior to randomization to HT and 18, 36, and 48 months after randomization to HT). KEEPS-Cog testing sessions coincided with visits for the parent KEEPS trial. The current manuscript includes measures ascertained at the baseline study visit only, prior to randomization to treatment and thus hormone levels reflect only endogenous levels.

Participants

Recruitment and enrollment from the parent KEEPS trial into the KEEPS-Cog sub-study are described in Figure 1. Seven hundred twenty-seven women were randomized in the parent KEEPS trial. Of these, 693 participated in the KEEPS-Cog study. KEEPS-Cog participants were recently menopausal women (42–59 years old) and between 6 months and 3 years of their last menses. Participants included women without known or suspected cognitive or cardiovascular disease, and meeting the inclusion criteria for KEEPS (KEEPS-Cog NCT000154180) enrolled at one of nine clinical testing sites. KEEPS is a multicenter, randomized, double-blinded, placebo-controlled trial, designed to test the hypothesis that low-dose HT initiated in recently postmenopausal women will reduce the progression of subclinical atherosclerosis as measured by carotid artery intima-media thickness (CIMT) and coronary artery calcification (CAC) over four years [19, 20].

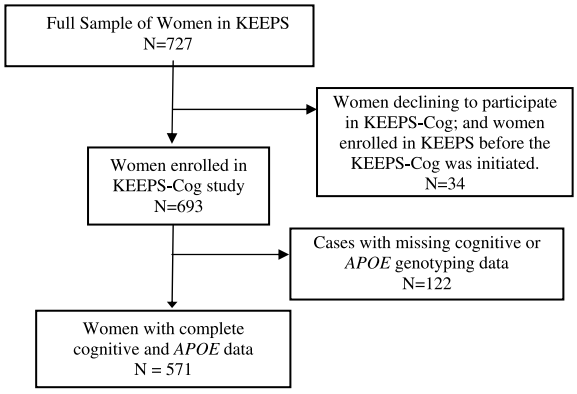

Fig. 1.

Potential participants underwent a depression and cognitive dysfunction screening, a medical examination, blood tests, and an electrocardiogram at baseline. Women scoring 18/63 or greater on the Beck Depression Inventory, or reporting suicidal ideation as assessed by the Beck Depression Inventory, or scoring 22/30 or lower on the Mini-Mental State Exam were excluded from the KEEPS-Cog study. All women underwent a high-resolution B-mode ultrasound examination for the assessment of CIMT and computed tomography for the assessment of CAC [21]. Women were also excluded if they had a history of clinically defined cardiovascular disease; were current heavy smokers (more than ten cigarettes/day by self-report); their CAC score was ≥ 50 Agatston units (AU); body mass index (BMI) was $> 35\,kg/m^2$; or if they had dyslipidemia (low-density lipoprotein (LDL) cholesterol > 190 mg/dL), hypertriglyceridemia (>400 mg/dL), serum 17β-estradiol>40 mg/dL, uncontrolled hypertension (systolic BP > 150 mmHg or diastolic BP > 95 mmHg), or fasting blood glucose (FBG)>126 mg/dL [19]. Women using lipid-lowering medications at baseline were excluded. KEEPS-Cog was approved by Institutional Review Boards at each of the nine clinical testing sites and the University of Wisconsin (UW) in Madison. All participants provided written informed consent.

Cognitive task measures

Cognitive tasks included the Modified Mini-Mental State Exam [22], Prospective Memory Test [23], NYU Paragraph Recall [24], Stroop Color Word Interference Test [25], Letter-Number Sequencing [26], Digit Symbol [27], Trail Making Test (Trails A & B) [28], the California Verbal Learning Test (CVLT-II) [29], the Benton Visual Retention Test [30], Digit Span [26], and Verbal Fluency [28]. We combined components of the individual cognitive tests into a four-factor structure for analyses described below.

Laboratory values and vascular risk factors

Blood pressure was taken in the morning by a registered nurse experienced in BP measurement methodology. Participants were seated for five minutes before BP was taken. A conventional mercury

sphygmomanometer, appropriate sized BP cuff, and a stethoscope with a bell were used. Two BP determinations were obtained from the same arm, ten minutes apart. The average of the two BP readings was used for analyses. Venous blood samples were obtained from the arm opposite of and after measurements of BP. Low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides, and blood glucose (FBG) were measured by Kronos Science Laboratories (Phoenix, AZ).

Apolipoprotein E (APOE) genotyping

APOE genotype was determined from DNA extracted from venous blood samples as previously described [31]. Briefly, DNA was amplified by polymerase chain reaction using specific primers for the *APOE* gene. The DNA was then sequenced and analyzed for genotype using the FinchTV program (Version 1.3; Geospiza, Inc).

Hormone analyses

Serum estradiol, estrone, testosterone, and progesterone were measured at the University of Wisconsin's Clinical and Translational Science Award (CTSA) – funded Institute for Clinical and Translational Research (ICTR) laboratory in the Assay Services Core. After sample preparation through extractions, the steroids were separated from each other by liquid chromatography and measured as their mass-to-charge ratio through mass spectrometry (LC/MS). Baseline samples were batched and assays were conducted at one time. The method consisted of monitoring the steroids simultaneously with their internal standards for peak identification and analyses. Ultrapure water (500 µl) with 40 µl of internal standards (deuterated steroids: testosterone, estradiol, estrone, progesterone; CDN Isotopes in Pointe-Claire, Quebec, Canada) were added to 400 µl of serum and extracted with 2 ml of methyl ether. The ether layer was dried and re-suspended in ethanol and 500 µl water and 1 ml of dichloromethane. The dichloromethane portion was dried and re-suspended in 25 µl acetonitrile/water (50 : 50). To derivatize the estrogens, 25 µl dansyl chloride was added, heated for 3 min and samples were prepared for injection of 30 µl into the LC/MS. A 150x2.10 mm column (2.6 µ, C18, Kinetex, Phenomenx, Torrance, CA) was used for the HPLC separation on our Agilent 1100 series system. Positive ion identification was used for testosterone (m/z 289), progesterone (m/z 315), estradiol (m/z 506), and estrone (m/z 504) measurements. Separation was performed by using a gradient in mobile phase $B = 95\%$ acetonitrile (ACN)/5% water (H_2O), and A 95% H_2O/5% ACN where %B begins at 44%, increases to 60% at 10 min, to 90% at 16 min and back to 70% at 20 min, to 44% at 23 min. Flow rate was 100 µl/min. Coefficients of variation for sex hormones assayed in the present study are as follows: testosterone (18.8%); progesterone (25.3%); estradiol (12.9%); and estrone (22.4%).

Statistical analyses

All analyses were conceived before the KEEPS Cog study began and were approved by all KEEPS Investigators. All analyses were controlled for age, education, race, testing site, and *APOE* $\varepsilon 4$ status based on the reported independent effects of *APOE* on cardiovascular risk and cognitive task performance [32].

Given the large number of cognitive variables, we conducted a confirmatory factor analysis (CFA) to derive summary scores. Compilation of factor scores comprised of components of the nine cognitive tests is illustrated in Figure 2 and has been published previously [33]. Using standard criteria for model fit [34] a four-factor solution provided an acceptable fit ($\chi^2 = 360.58$ with a p-value <0.001; comparative fit index - CFI = 0.92, root mean squared error of approximation-(RMSEA)=0.038). The four cognitive domains used in the analyses included 1) Verbal Learning; 2) Auditory Attention & Working Memory; 3) Verbal Attention & Executive Function; and 4) Speeded Language & Flexibility. The factor scores served as outcome measures in the mixed regression models. The model was estimated using the R package.

To explore the relationship between vascular risk factors and cognitive factor scores, we employed a linear mixed effect modeling approach. Vascular risk factors entered into the model included systolic BP, LDL-C, HDL-C, FBG, and BMI as well as CIMT and CAC. We controlled for age, race, education level, and *APOE* $\varepsilon 4$ status. All p values were set at 0.05 and were adjusted for multiple comparisons using Benjamini-Hochberg's procedures [35].

In order to investigate a potential impact of endogenous hormone levels on the systolic BP – cognition relationship, we next employed another linear effects model. In this model, we included endogenous sex hormone levels including estradiol, estrone, testosterone, and progesterone. As was the case with the first model, we controlled for age race, education level, and *APOE* $\varepsilon 4$ status, p values were set at 0.05, and we adjusted for multiple comparisons.

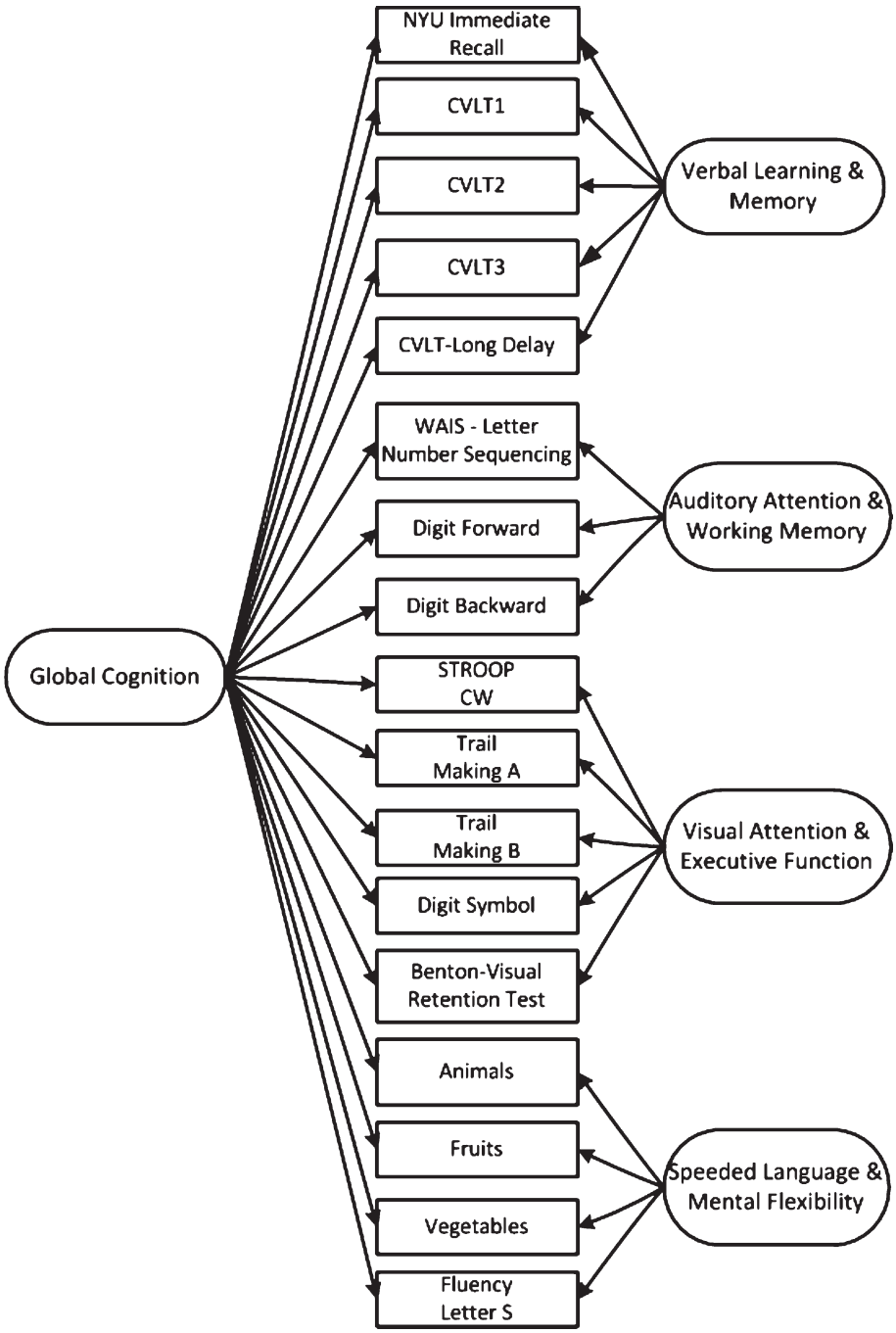

Fig. 2. Factor structure summarizing cognitive variables. Seventeen variables from nine tests were condensed into four independent specific factors. CVLT1-3 Represent the learning trials component of the California Verbal Learning Test.

PROCEDURES

Administration of the cognitive battery was conducted by trained psychometricians at each of the nine testing sites. Before the KEEPS-cog sub-study initiated, all psychometricians took part in a two-day group training covering KEEPS-Cog rationale, methodology, test administration and scoring, and a full day of interactive, mock cognitive and affective testing. Each site was provided with a cognitive testing manual and

instructions for test administration and scoring and a DVD of a mock testing session. In the instance of psychometrician turnover, the KEEPS-Cog coordinator, a trained cognitive neuroscientist at the UW Madison, traveled to the testing site and trained the new psychometrician on test administration and scoring. Additionally, we conducted training sessions every two years and quarterly conference calls were held between the UW Madison and all sites to ensure project continuity. To further ensure the quality of the data, 10% of participant data at each testing site was audited to ensure correct test scoring and data entry. Quality assurance checks exceeded 98% accuracy for all sites for all cognitive variables.

The KEEPS-Cog testing session lasted approximately 1.5 h. The cognitive testing area was free of excessive noise and approved by the KEEPS-Cog study personnel at the UW Madison. Because the KEEPS-Cog visit coincided with the parent KEEPS visits that required a fasting blood draw, all participants were tested in the morning and were given a light breakfast before cognitive testing began. All participants were tested by the same psychometrician at their respective site. Order of neuropsychological test administration was consistent across sites and tests were grouped to minimize between test interference. Tests were scored and entered into a centralized database within 3 days of the visit.

RESULTS

Participants

A detailed description of KEEPS-Cog participant enrollment is illustrated in Figure 2. Of the 693 women meeting inclusion criteria for KEEPS and consenting to participate in the KEEPS-Cog, 122 were excluded from the present analyses due to missing cognitive data or unwillingness to take part in testing for *APOE* genotyping.

Demographic information for participants enrolled in the KEEPS-Cog sub-study is listed in Table 1. Participants ($n = 571$) were middle aged (mean 52.7 years, range 42–59 years), physically healthy and well-educated, with 73.8% reporting at least some college education. The majority of participants identified as White (78.1%). Those identifying as Black or Hispanic were 7.1% and 6.2%, respectively. Percentage of Non-White, non-Hispanic participants from each of the nine clinical testing sites ranged from 5.6% to 17.7% of the total sample.

Table 1
Demographic information of KEEPS-Cog participants

Education	*n*	%
Some High School	3	0.5
High School Diploma or GED	46	7.0
Some College/Vocational School	122	18.7
College Graduate	263	40.3
Some Graduate or professional school	30	4.6
Graduate or Professional degree	189	28.9
Site		
Brigham and Women	81	12.3
Columbia	87	13.2
Mayo	117	17.7
Albert Einstein	69	10.4
University of California	51	7.7
Utah	90	13.6
Washington	37	5.6
Yale	67	10.1
Kronos	62	9.4
Race		
No Answer	36	5.4
Asian/Indian	4	0.6
Black	47	7.1
White	516	78.1
Chinese	6	0.9
Philipino	2	0.3
Hispanic	41	6.2
Japanese	1	0.2
Korean	1	0.2
Other	7	1.1

Table 2 shows KEEPS-Cog participants' vascular risk factors. By design, the middle-aged sample is very healthy and at low risk for vascular disease based on BP measures, BMI, and HDL-C, LDL-C, and FBG levels. Percent of women enrolled in KEEPS-Cog with an *APOE* $\varepsilon 4$ allele is 14.3%. There is no significant difference on any measure between KEEPS-Cog participants and participants enrolled in the parent KEEPS study.

Results of the fixed effects models are shown in Table 3. Results reveal a significant association between systolic BP and the attention and working memory factor score ($p = 0.004$) after controlling for age, education, and *APOE* $\varepsilon 4$ status. This relationship, however, fades after adjusting for multiple comparisons (adjusted, $p = 0.10$). Additional analyses showed no relationship between BP and the other three factor scores.

To ensure the relationship between systolic BP and cognition was not attributed to endogenous sex hormone levels, we entered estradiol, estrone, progesterone, and testosterone into a fixed effects model. Analyses show that the relationship between the auditory working memory factor score and systolic BP was not altered after including baseline sex hormones (all p values > 0.28) (See Table 4).

Table 2
Description of vascular risk factors among women in the KEEPS-Cog study

Vascular risk factor	Mean	SD
Age (years)	52.66	2.59
Height (ft)	5.45	2.40
Weight (lbs)	155.60	26.60
Waist Circumference (in)	33.32	6.82
Average systolic (mm/Hg)	118.58	15.25
Average diastolic (mm/Hg)	74.61	9.24
Body mass index (kg/m²)	26.32	4.31
Fasting blood glucose (mg/dL)	89.17	9.77
Triglycerides (mg/dL)	91.75	51.41
LDL-C (mg/dL)	128.99	29.73
HDL-C (mg/dL)	64.66	17.13
CIMT	0.72	0.09
CAC	1.33	5.18
Current Tobacco Use (% users)	6.4%	
Current Alcohol Use (% users)	73.6%	
APOE ε4 (% E4 positive women)	14.3%	

LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; CIMT, carotid artery intima-media thickness; CAC, coronary artery calcification.

Table 3
Results of the mixed effects model describing the relationship between the auditory attention and working memory factor score and vascular risk factors and subclinical atherosclerosis measures of carotid artery intima-media thickness (CIMT) and coronary artery calcification (CAC). Age, education, race and *APOE* ε4 status were entered as covariates

Attention/Working Memory	*t*-value	*p*-value	Estimates	SE	DF
Systolic Blood Pressure	–2.93	0.004	–0.0020	0.0007	521
CIMT	0.533	0.594	0.0649	0.1217	521
CAC	–0.778	0.436	–0.0016	0.0021	521
LDL-C (mg/dL)	–0.225	0.821	–0.0001	0.0003	521
HDL-C (mg/dL)	–0.345	0.730	–0.0002	0.0006	521
Fasting blood glucose (mg/dL)	0.807	0.420	0.0009	0.0011	521
Body mass index	0.737	0.460	0.0018	0.0025	521

LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.

DISCUSSION

Our results show that the KEEPS-Cog cohort was healthy and free of major medical conditions and comorbidities at baseline. As such, our results are less prone to confounding related to concomitant vascular and cognitive interference. Our main result was a relationship between auditory attention/working memory and systolic BP such that participants with higher systolic BP (still within the normotensive range) performed worse on tests within this domain. While our findings are largely negative, results suggest that certain vascular risk factors (i.e., BP) may be more sensitive to cognitive task performance than other vascular risk factors, among healthy, middle aged, recently menopausal women.

Present results are consistent with other studies showing that higher BP is associated with poorer cognitive performance [36]. A number of studies have demonstrated that midlife hypertension has a negative impact on cognitive performance [37], is an established risk factor for AD [38], and has been linked to increased cognitive impairment among AD patients [39]. Hypertension has been linked to deficits in attention [40] and memory [41], the factor score found to be related to BP in the present study. The auditory attention/working memory factor score is comprised of digit span forward, digit span backward, and the letter number sequencing task. Prior research has shown that the individual components of the attention/working memory factor score, particularly digit span, have been linked to BP dysregulation during midlife [42, 43].

Our data revealed that the relationship between BP and cognition was not influenced by endogenous sex hormone levels (p values > 0.28) for estradiol, estrone, testosterone, and progesterone. This result is consistent with prior results linking hypertension to cognitive impairment and mild cognitive impairment incidence, independent of the effects of endogenous estrogen levels or HT administration [44, 45]. These results suggest that subtle increases in BP may influence cognition, independent of estrogen's effects on cognition and disease incidence. It is likely that both increased midlife vascular risk factors and the loss of estradiol during the menopausal transition serve as independent risk factors that work synergistically to increase the risk for cognitive decline and incident AD in later life.

Table 4
Results of the mixed effects model describing the relationship between the auditory attention and working memory factor score and sex hormone levels

Serum hormone levels	Mean (SD)	*t*-value	*p*-value	Estimates	SE	DF
Estradiol, pg/mL	21.7 (30.9)	0.81	0.42	0.0004	0.0005	446
Estrone, pg/mL	23.8 (16.7)	–1.03	0.29	0.0010	0.0010	446
Testosterone, pg/mL	217.8 (128.3)	–0.60	0.54	–0.0000	0.0001	446
Progesterone, pg/mL	355.7 (288.8)	1.00	0.31	0.0000	0.0000	446

A potential limitation of the current data is that the KEEPS-Cog study cohort primarily identifies as White, though the study as a whole is more representative than the Women's Health Initiative (WHI) or the Women's Health Initiative Memory Study (WHIMS) [46]. Black and Hispanic populations are more likely to be afflicted with increased risk for hypertension across the lifespan than White participants. Also, while we intentionally enrolled only healthy women into the sample to prevent interference, the results derived from this and other KEEPS publications may not extend to less healthy populations. The KEEPS trial employed clinical BP readings as opposed to the now recommended 24 h ambulatory methodology. In the future, trials BP assessment should employ ambulatory BP methodologies, as they are less susceptible to white coat hypertension and isolated hypertension. Last, participant medication data is currently undergoing a rigorous categorization process and was therefore not available for analyses here. While the KEEPS only enrolled participants who were healthy in regard to cardiovascular and psychological measures, future analyses will need to account for this variable, as some medications are known to have cognitive and cardiovascular effects.

Midlife hypertension has been associated with decreasing estradiol levels during menopause and cognitive impairment. Hypertension during midlife has also been associated with an increased risk of AD in later life, while reductions in BP are associated with protection against AD [11, 47]. This indicates that long-standing, uncontrolled BP may contribute to AD neuropathology, possibly through decreased cerebral blood flow and accumulation of Aβ, a key pathological feature of preclinical AD [11]. For instance, plasma $A\beta_{42}$ has been shown to be significantly and positively correlated with systolic and diastolic BP and pulse pressure [48], and the Honolulu Heart Program/Honolulu-Asia Aging Study reported that midlife systolic BP variation is associated with increased Aβ in the hippocampus [49]. Moreover, studies involving BP medications suggest that some antihypertensives reduce the risk for AD and improve cognition in patients with AD via improved cerebral blood flow [50–52]. Although collectively, these studies suggest that cognition is impaired in the presence of prolonged uncontrolled hypertension and the mechanism driving this relationship may be directly related to AD neuropathology. Future studies investigating the relationship between midlife cognition and BP would likely benefit from the inclusion of neuroimaging and measures of potential soluble or cellular biomarkers in order to assess the potential mechanisms driving this relationship.

It should be noted that our prior work [16] as well as other studies [17] have shown that even subclinical vascular dysfunction, (e.g., slightly high or low BP), may pose a significant additional risk factor for cognitive decline and AD, compounded by genetics and family history. While our participants were normotensive, we observed a relationship between higher systolic BP and poorer cognitive task performance in a healthy, middle-aged cohort. In contrast to prior HT trials, the healthy KEEPS-Cog cohort is ideally positioned to address this important issue, as the participants do not have clinical evidence of cognitive or vascular disease at baseline. Surprisingly, we did not observe a relationship between BP and the remaining three cognitive factor scores, or between cognition and any of the other vascular risk factors, which is why we report the current results as largely negative. It is likely that the exceptional vascular health of our participants at baseline did not allow for enough power to detect the impact of subtle, preclinical vascular differences on our clinical outcomes. That we did detect a weak relationship between BP and cognition may suggest that this particular vascular risk factor may be more sensitive to the cognitive effects of preclinical fluctuations within healthy limits. Future analyses of the KEEPS-Cog will determine if HT administration or endogenous hormone levels (i.e., placebo) are related to vascular risk factors over time.

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Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2032).

IRB NUMBERS FOR KEEPS INSTITUTIONS

The central KEEPS and Phoenix KEEPS (IRB protocol by the Western IRB): STUDY NUM: 1058663 and WIRB PRO NUM: 20040792KEEPS (main study & cognitive substudy) #10-02980 and MDBHAS #11-05383; Brigham and Women's Hospital (Partners): #2004-P-002144 BWH; Mayo Clinic: 2241-04; Columbia: IRB#: AAAA-8062; Yale: 0409027022; University of Utah: 13257; Einstein/Montefiore: 04-08-213; University of Wisconsin: H-2005-0059; UCSF: KEEPS (main study & cognitive substudy) #10-02980; University of Washington IRB #26702; VAPSHCS IRB #01048.

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ADDITIONAL CONTRIBUTIONS

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